AR201-13102

COURTNEY M. PRICE
VICE PRESIDENT
CHEMSTAR

American Chemistry Council *Good Chemistry Makes It Possible*

June 28, 2001

Honorable Christine T. Whitman
Administrator, U.S. EPA
P.O. Box 1473
Merrifield, VA 22116

RE: Chemical Right-to-Know Program - Assessment Plan and Robust Summaries for the Acetic Acid and Salts Category, Registration Number

Dear Administrator Whitman:

The American Chemistry Council Acetic Acid and Salts Panel (Panel) submits for review and public comment its assessment plan report and robust summaries for the Acetic Acid and Salts Category under the U.S. Environmental Protection Agency's (EPA) High Production Volume Chemical Challenge Program. The Panel members are listed in the assessment plan report. Included in this package is a computer diskette that contains electronic copies of the assessment plan and robust summaries.

The Panel understands that there will be a 120-day review period for the assessment plan report and that all comments generated by, or provided to, EPA will be forwarded to the Panel for consideration.

Thank you in advance for attention to this matter. If you have any questions regarding the assessment plan report or robust summaries, please contact Laurie Miller, the Panel Manager. She can be reached at 703-741-5611 (telephone), 703-741-6091 (telefax) or laurie_miller@americanchemistry.com (email).

Sincerely yours,

MR 49480

U.S. HIGH PRODUCTION VOLUME (HPV) CHEMICAL CHALLENGE PROGRAM

ASSESSMENT PLAN

For

ACETIC ACID AND SALTS CATEGORY

Prepared by
American Chemistry Council
Acetic Acid and Salts Panel

June 28, 2001

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I. INTRODUCTION

The High Production Volume (HPV) Challenge Program is a voluntary initiative with an objective of completing screening level hazard data profiles for approximately 2800 HPV chemicals as identified on the US Environmental Protection Agency's (USEPA) 1990 Toxic Substances Control Act (TSCA) Inventory Update Rule (IUR). In the US, HPV chemicals are those that are manufactured or imported in quantities greater than 1 million pounds per year. The hazard data to be provided in the program are those that meet the requirements of the Screening Information Data Set (SIDS) Program (OECD 1997a). SIDS, which has been internationally agreed to by member countries of the Organization for Economic Cooperation and Development (OECD), provides the basic screening data needed for an initial assessment of the physical-chemical properties, environmental fate, and human and environmental effects of chemicals. The information for completing the SIDS can come from existing data, may be generated as part of the HPV Challenge Program or may be provided through structure activity or category-based analyses. Once the available studies are identified or conducted, "robust summaries" are prepared.

The USEPA, Industry, and Non-Governmental Organizations (NGOs) are unified in their commitment to minimize the numbers of animals tested in the HPV Challenge Program whenever it is scientifically justifiable (USEPA 1999a, 1999b). Evaluating closely related chemicals as a group, or category, rather than solely as individual chemicals is one way to accomplish this goal. The use of categories is encouraged by USEPA in the HPV Challenge Program. Appropriately constructed categories allow for a more efficient evaluation while reducing the number of animals required for testing.

In accordance with the HPV Challenge Program, the Acetic Acid and Salts Panel (Panel), housed at the American Chemistry Council, is sponsoring a category that includes acetic acid and its salts as well as related acids and their salts. The Panel is comprised of the following companies:

A.E. Staley Manufacturing Company
Millennium Chemicals Incorporated
Cargill, Inc.
Archer Daniel Midland Company
The Procter and Gamble Company
Vulcan Chemicals
W.R. Grace & Company
Mallinckrodt Inc.
Eastman Kodak Company
Eastman Chemical Company
Sterling Chemicals
Celanese Ltd
OMG Americas, Inc.
The Shepherd Chemical Company

This assessment plan provides a summary and analysis of the available data, and identifies areas where additional data may be needed. Section II of this assessment plan provides a rationale and justification for the development of the Acetic Acid and Salts category. Section III reviews the methods used in the collection of published and unpublished data. Section IV reviews the evaluation of data quality. Section V reviews the preparation of the robust summaries and the construction of a data matrix. Section VI is an in-depth evaluation of data matrix patterns for each of the four data endpoint categories (i.e., physical-chemical properties, environmental fate, ecotoxicity and toxicity). Section VII is a summary of the Acetic Acid and Salts category and its properties. Section VIII presents the conclusions regarding data availability and the need for additional testing to complete the SIDS profiles for the sponsored compounds.

II. IDENTIFICATION OF THE STRUCTURE BASED CATEGORY

The Panel is sponsoring a total of 13 individual compounds, the structures of which are shown in Appendix 1. The category includes several food acids and their corresponding salts, specifically acetic acid and its ammonium, calcium, potassium, sodium, magnesium, and manganese salts; citric acid and its sodium, tripotassium and trisodium salts; fumaric acid; and malic acid[1]. These compounds are grouped together because of their close structural relationships, their natural occurrence in plants and animals, and their fundamental role in cell metabolism, particularly in the tricarboxylic acid cycle (also known as the citric acid or Kreb's cycle), which is where humans get their energy. These compounds are all carboxylic acids or their respective salts. As shown in Appendix 1, acetic acid has one, fumaric acid and malic acid have two, and citric acid has three carboxylic acid functional groups. Malic acid and citric acid also have an additional alcohol group.

Role in the Citric Acid Cycle

Food acids, such as acetic acid, citric acid, fumaric acid, and malic acid (and citrate, fumarate and malate), are found in a wide variety of unprocessed foods. The last three acids play key roles in the metabolic energy system called the Citric Acid Cycle or Kreb's Cycle (Gardner 1966). The cycle consists of a series of chemical reactions occurring within the cell that are responsible for the final breakdown of food molecules to form carbon dioxide, water, and energy. This process is active in all animals and higher plants and is carried out in the mitochondria.

The cycle is the major pathway by which animals obtain their required energy, and three of these food acids (citric, fumaric and malic) are integral components in this series of enzymatic reactions. A key feature of the cycle is that the citric, fumaric and malic acids are used over and over again in the production of energy. Furthermore, these acids catalytically accelerate oxygen uptake and the production of carbon dioxide by muscle and other tissues. They are not found in appreciable

[1] Note that the salts may be referred to by synonyms in some sources. For example, acetic acid ammonium salt is commonly called ammonium acetate. Similarly, citric acid tripotassium salt is commonly called potassium citrate (or tripotassium citrate).

quantities among the waste products, as elimination by animal kidneys tends to increase their consumption by the respiratory reactions, thus maintaining an "acid-base" balance within the animal system (Gardner 1966).

In summary, the compounds in this category are naturally occurring in foods and essential to normal metabolic processes. They are also commonly used as flavor and texture enhancers in a wide variety of foods. The compounds in this category can be viewed as biochemically and toxicologically equivalent to their naturally occurring counterparts.

III. COLLECTION OF PUBLISHED AND UNPUBLISHED DATA

Panel members contributed in-house studies of physical-chemical properties, environmental fate and transport, ecotoxicity, and mammalian toxicity for the compounds in the category. To supplement the industry data, literature searches were conducted of on-line databases and CD-ROMs (e.g., Hazardous Substance Data Bank [HSDB], Registry of Toxic Effects of Chemical Substances [RTECS], Aquatic Toxicity Information Retrieval [AQUIRE]), standard scientific compendia (e.g., *CRC Handbook of Chemistry and Physics*, *The Merck Index*, *Patty's Industrial Hygiene and Toxicology*, *Handbook of Environmental Data on Organic Chemicals*, BIBRA toxicology profiles), and other published sources (e.g., International Uniform Chemical Information Database [IUCLID]). The literature search was augmented by investigating the web sites of a variety of government and regulatory organizations, such as the Agency for Toxic Substances and Disease Registry (ATSDR), Consumer Product Safety Commission (CPSC), Food and Drug Administration (FDA), and World Health Organization (WHO). The USEPA ECOTOX database was also searched. A number of primary references from peer reviewed published journals were also reviewed. The Syracuse Research Corporation EPIWIN v.2.2 model, which is accepted by the U.S. Environmental Protection Agency (USEPA) for organic compounds, was used to provide estimates of key physical-chemical properties for some of the compounds.

IV. EVALUATION OF DATA FOR QUALITY AND ACCEPTABILITY

The collected data were reviewed for quality and acceptability following the general USEPA and OECD SIDS guidance (USEPA 1999c; OECD 1997b) and the systematic approach described by Klimisch et al. (1997). These methods include consideration of the reliability, relevance and adequacy of the data in evaluating their usefulness for hazard assessment purposes. The Klimisch et al. (1997) approach specifies four categories of reliability for describing data adequacy. These are:

1 **Reliable without Restriction:** Includes studies or data complying with Good Laboratory Practice (GLP) procedures, or with valid and/or internationally accepted testing guidelines, or in which the test parameters are documented and comparable to these guidelines.

2 **Reliable with Restrictions:** Includes studies or data in which test parameters are documented but vary slightly from testing guidelines.

3 **Not Reliable:** Includes studies or data in which there are interferences, or that use non-relevant organisms or exposure routes, or which were carried out using unacceptable methods, or where documentation is insufficient.

4 **Not Assignable:** Includes studies or data in which insufficient detail is reported to assign a rating, e.g., listed in abstracts or secondary literature.

Only those studies which are deemed reliable for the current HPV Challenge Program purposes are included in the data set for this assessment plan. Reliable studies include both categories rated 1 (Reliable without restriction) and 2 (Reliable with restrictions). Studies rated 3 (Not reliable) were not used. Studies rated 4 (Not assignable) were used when professional judgment deemed it appropriate as part of a weight-of-evidence approach. Finally, some older studies were not included if they had been superceded by more recent studies rated 1.

V. ROBUST SUMMARIES AND CONSTRUCTION OF DATA MATRIX

Robust summaries were prepared according to the format recommended by the USEPA (1999d) and OECD (1997a) and constructed using Microsoft Word software. These summaries present the salient information from each of the reliable studies. All of the summaries are collected into a dossier that includes all of the individual acids and salts for the category. The dossier for the Acetic Acid and Salts category is a separate document that should be used in conjunction with this assessment plan.

The data in the robust summaries are used to construct a data matrix table. This table (Appendix 1 to this assessment plan) is a matrix of SIDS/HPV endpoints and the available data for each of the sponsored compounds in the Acetic Acid and Salts category. To facilitate the connection between data in the table and the corresponding robust summaries, reference sources have been included with each data point.

VI. EVALUATION OF MATRIX DATA PATTERNS

The data matrix table (Appendix 1) identifies where data for specific compounds and data endpoints are available (data provided) and not available (indicated by "--" in the table). The available data were evaluated for patterns and trends among the 13 compounds that could be used to predict values for a particular endpoint (e.g., acute oral toxicity) where adequate data are not available for a given compound (i.e., "Read Across"). In addition, the data were evaluated to determine to what extent the SIDS/HPV data endpoints were covered by available data for each compound in the category (i.e., "Read Down").

A. Evaluation of "Read Across" Patterns

The following discussion reviews the "Read Across" patterns among the 13 compounds for each of the four major data areas: physical-chemical properties, environmental fate and transport, ecotoxicity, and mammalian toxicity. The primary patterns to look for in the physical-chemical property data are similarities in the parameters that affect dissociation and partitioning between aqueous and organic phases. In reviewing the environmental fate data, the important information to look for is the primary mechanism of degradation or dissociation of the compounds. These factors also affect the bioavailability and aquatic toxicity of the compounds. Similarly, it is important to look for any trends or similarities in the mammalian toxicity data, which are important surrogates for potential human effects. Each of the four acids (acetic, fumaric, malic, and citric), along with their corresponding salts, are reviewed separately in the following sections.

Acetic Acid and its Salts

Acetic acid and its salts are comprised of seven compounds that include acetic acid ($H_4C_2O_2$), ammonium acetate ($H_7C_2NO_2$), calcium acetate ($H_6CaC_4O_4$), magnesium acetate ($H_6C_4MgO_4$), manganese acetate ($H_6C_4MnO_4$), potassium acetate ($H_3KC_2O_2$), and sodium acetate ($H_3NaC_2O_2$). The chemical structures, physical-chemical properties, environmental fate behavior, and aquatic and mammalian toxicity of these seven compounds are similar. Acetic acid and its salts undergo dissociation in aqueous media into the acetate anion ($H_3C_2O_2^-$) and the respective cations (H^+, NH_4^+, Ca^{2+}, Mg^{2+}, Mn^{2+}, K^+, Na^+). The toxicity of each compound is driven by acetate, with the cations playing a minor role.

Physical-chemical Properties

Reliable data exist for melting and boiling points, water solubility and pH for most of the seven compounds (see Appendix 1). With the exception of acetic acid, for which actual experimental data exist, octanol-water partition coefficient (Kow) and vapor pressure data are largely available as estimated values using the standard chemical property estimation software, EPIWIN v.2.2 (Syracuse Research Corporation 1993). All seven compounds are highly water soluble and of moderate to low volatility. Based on such information, the Panel believes that the available data adequately characterizes the physical-chemical properties of acetic acid and its salts.

Environmental Fate and Transport

Reliable data for environmental fate and transport behavior are available for acetic acid and its salts (see Appendix 1). Biodegradation appears to be the most significant removal mechanism. These compounds readily dissociate into their respective cations and the acetate anion; the anion is subsequently biodegraded. Data indicate that acetic acid and sodium acetate (acetic acid, sodium salt) photodegrade, although the rate is substantially slower than that of biodegradation. Level I fugacity modeling predicts that about 73% of any acetic acid

released to the environment would partition to water, with the remainder partitioning into the air. These data demonstrate that acetic acid and its salts are not persistent in the environment. The Panel believes that the available data and analogous behavior of the compounds can be used to adequately characterize the environmental fate and transport properties of acetic acid and its salts.

Ecotoxicity

Reliable ecotoxicity data for aquatic animals are available for four of the seven compounds (see Appendix 1). The ecotoxicity data indicate that these compounds are practically nontoxic to only slightly toxic. The three remaining salts (calcium, magnesium and manganese) are closely related to the other salts in structure and behavior and so would be expected to have low toxicity as well. Of the seven compounds, acetic acid appears more toxic, which is attributable to its relatively low pH. Toxicity data for algae are available for acetic acid and its sodium salt, and also indicate generally low toxicity. While some of these compounds lack actual data, the Panel believes that the available aquatic toxicity data and the generally low to moderate toxicity of acetic acid and its salts adequately characterize the ecotoxicity of these compounds.

Mammalian Toxicity

Several aspects of mammalian toxicity are evaluated. Acute testing provides information on gross effects, such as mortality, from exposure to high doses. Repeated dose testing provides information on toxicity associated with multiple doses over time. Genetic testing is conducted to evaluate the potential for mutagenic effects by using bacterial systems (e.g., the Ames test), non-bacterial systems (e.g., chromosomal aberrations), and *in vivo* (i.e., live animal) systems. Reproductive and developmental/teratogenic testing provides information on the potential effects of long-term exposure to lower doses, especially as related to possible effects in developing embryos and young animals. It is important to note that the lack of significant exposure may obviate the need to fill apparent data gaps with mammalian testing.

The available data indicate that acetic acid and its salts have generally low acute mammalian toxicity (see Appendix 1). Acute oral toxicity data for mammals are available for all compounds with the exception of the ammonium salt. Acute inhalation data are available for acetic acid and the sodium salt. Inhalation is not expected to be a primary route of exposure given that acetic acid and its salts have generally low volatility and are highly soluble. Dermal toxicity data are available only for acetic acid, but the level of toxicity is low and the salts are expected to exhibit a comparable dermal safety profile. Several studies indicate that the acute toxicity via other routes of exposure (i.e., intravenous, subcutaneous, intraperitoneal, etc.) is also low. Thus, additional acute testing on the other compounds is not deemed by the Panel to be necessary to characterize this category.

There are repeated dose, genetic, and developmental/teratogenic toxicity test endpoints for acetic acid. An essentially complete set of data for the sodium salt of acetic acid also is available. Less data are available for the other salts, but the data that are available show similar responses to the sodium salt. The dissociative nature of salts suggests that additional testing would provide no information useful for assessing the hazard of this category. Of note, none of the counter ions is expected to impact the overall safety profile of the salts within this chemical category.

In addition, acetic acid is naturally occurring as the acid in apple cider vinegar and other fruit-derived products. It and several of its salts are commonly used as food additives (e.g., as flavor enhancers) and are listed as Generally Recognized as Safe (GRAS) by the USFDA. Given the lack of significant toxicity, the natural occurrence in both plants and animals, and the common use in foods, the Panel believes that no additional mammalian toxicity testing is necessary.

Fumaric Acid

While acetic acid is the simplest form and contains only a single carboxylic acid unit, fumaric acid ($H_4C_4O_4$) contains two carboxylic acid units connected by a double bond.

Physical-chemical Properties

Reliable data are available for all of the SIDS/HPV data elements and indicate that fumaric acid is highly soluble in water and has low volatility. Level I fugacity modeling predicts that virtually all (99.8%) of any fumaric acid released to the environment would partition to water. The Panel believes that the available data adequately characterize the physical-chemical properties of fumaric acid.

Environmental Fate and Transport

Reliable data are available for all the SIDS/HPV data elements. Fumaric acid dissociates into H^+ and fumate ($H_3C_4O_4^-$) and fumate undergoes significant degradation by both biotic and abiotic mechanisms and is therefore not persistent. Nearly complete biodegradation was observed after 21 days under aerobic conditions. The Panel believes that the available data adequately characterize the environmental fate and transport properties of fumaric acid.

Ecotoxicity

Likewise, complete data are available for all the SIDS/HPV aquatic toxicity data elements. LC_{50} values for fish and *Daphnia* were greater than 200 mg/L. The value for the more sensitive algae was 41 mg/L. These data indicate that fumaric acid has low toxicity to aquatic animals and plants.

Mammalian Toxicity

Acute oral and dermal toxicity data indicate that fumaric acid is of low acute toxicity, with LD50 values from approximately 10 g/kg bw (oral) to greater than 20 g/kg bw (dermal). *In vitro* and in vivo studies were negative with regards to genetic toxicity. Reproductive and developmental/teratogenic toxicity studies also resulted in no indication of these effects after exposure to fumaric acid. The Panel believes that the large amount of available data and the low toxicity indicated are adequate to characterize the mammalian toxicity of fumaric acid.

In addition, fumaric acid is naturally occurring in apples, beans, carrots and other fruits and vegetables. It is also commonly used to control pH and produce light textures in such foods as cake, cookies and soft drinks. Fumaric acid is listed as GRAS by the USFDA.

Malic Acid

Malic acid ($H_6C_4O_5$) is very similar to fumaric acid, with the difference being the addition of a hydroxyl group (OH) and removal of a double bond.

Physical-chemical Properties

Reliable data are available for all of the SIDS data elements and indicate that malic acid is highly soluble in water and has a low volatility. Based on such information, the Panel believes that the available data adequately characterize the physical-chemical properties of malic acid.

Environmental Fate and Transport

Photodegradation and biodegradation data are available for malic acid and show that it dissociates into H+ and malate ($H_5C_4O_5^-$). Malate has been shown in a series of screening tests to biodegrade readily in soil and water. Level I fugacity modeling predicts that 100% of any malic acid released to the environment would partition to water. Based on such information, the Panel believes that malic acid is not persistent in the environment and is adequately characterized.

Ecotoxicity

Data on the aquatic toxicity of malic acid to daphnids are available. No data on toxicity to fish and algae were available, but the 48 hour LC_{50} for *Daphnia magna* was 240 mg/L, indicating a low level of aquatic toxicity. Given this data and the considerable aquatic toxicity data for the structurally related compounds in this category (e.g. acetic, fumaric and citric acids), no further aquatic tests are deemed by the Panel to be necessary.

Mammalian Toxicity

Acute data for the oral and intraperitoneal exposure routes are available for malic acid and indicate a low to moderate toxicity. Dermal toxicity data are not available for malic acid, but are expected to be comparable to the relatively low order of dermal toxicity associated with fumaric acid. *Both in vitro* and *in vivo* studies demonstrated no evidence of genetic toxicity. Developmental/teratogenic toxicity studies also resulted in no indication of these effects after exposure to malic acid. The Panel believes that the large amount of available data, combined with the low toxicity, are adequate to characterize the mammalian toxicity of malic acid.

In addition, malic acid occurs naturally as the major acid in apples, apricots, cherries, broccoli, carrots, potatoes, and many other fruits and vegetables. It is also commonly used as a flavor booster in candy, jelly, fruit drinks and ice cream. It is listed as GRAS by the USFDA.

Citric Acid and its Salts

Citric acid and its salts are comprised of four compounds, which include citric acid ($H_8C_6O_7$), sodium citrate ($H_7NaC_6O_7$), tripotassium citrate ($H_5K_3C_6O_7$), and trisodium citrate ($H_5Na_3C_6O_7$). The chemical structures and available data indicate that the physical-chemical properties, environmental fate behavior, and aquatic and mammalian toxicity of these four compounds are similar. As in the case of the other acids and salts in this category, citric acid and its salts undergo dissociation in aqueous media into the citrate anion ($H_7C_6O_7^-$) and the respective cations (K^+, Na^+). The toxicity of each compound is driven by citrate, with the cations playing a minor role. Therefore, where data are available for any of the compounds within this sub-category, they are considered by the Panel to be adequate to represent the entire group.

Physical-chemical Properties

Reliable data exist for all relevant physical-chemical properties for citric acid and its tripotassium and trisodium salts. These compounds are all highly water soluble and of moderate to low volatility. The Panel believes that the available data adequately characterizes the physical-chemical properties of citric acid and its salts.

Environmental Fate and Transport

Data on the environmental fate of citric acid and its trisodium salt are available. These data indicate that citric acid and its salts dissociate into their respective cations and the citrate anion, which is subsequently biodegraded. Studies indicate that citric acid and its trisodium salt are readily biodegraded (90-98% degradation after 48 hours). Level I fugacity modeling predicts that 100% of any citric acid released to the environment would partition to water.

Therefore, the existing data indicates that citric acid and its salts are not persistent in the environment. Collectively, these data are adequate, in the Panel's opinion, to characterize the environmental fate and transport properties of the group.

Ecotoxicity

Aquatic toxicity data for fish, *Daphnia* and algae are available for citric acid and its trisodium salt and indicate that these compounds have very low toxicity. With LC_{50} values ranging from 120 to 1,526 mg/L, citric acid is considered to be of low aquatic toxicity. The toxicity that is exhibited is most likely attributed to pH. The salts exhibit even less toxicity. The Panel believes that the available data and the structural similarities adequately characterize the ecotoxicity of citric acid and its salts.

Mammalian Toxicity

The available data indicate that citric acid and its salts have generally low mammalian toxicity. Oral toxicity data for mammals are available for citric acid and its sodium salt and demonstrate low toxicity. Dermal toxicity studies indicate that these compounds are moderate contact irritants. Acute toxicity from other routes of exposure (i.e., intravenous, subcutaneous, intraperitoneal, etc.) are available for all four of the citric acid and salts and confirm the low toxicity. Repeated dose studies available for citric acid and its sodium salt resulted in no adverse effects. *In vitro* bacterial studies were negative for genotoxicity for citric acid and its sodium and tripotassium salts. An *in vivo* cytogenetics study with citric acid also indicated no genetic toxicity. Finally, reproductive and developmental/teratogenic data are available for citric acid and its sodium salt. While body weight and survival time were effected at high doses of citric acid, no reproductive, developmental or teratogenic effects were observed in tests with either the citric acid or its sodium salt. The Panel believes that the available data and analogous structures and behaviors are adequate to characterize the toxicity for citric acid and its salts.

In addition, citric acid occurs naturally in all citric fruits, beans, tomatoes, and many other fruits and vegetables. It is also listed as GRAS by the USFDA and is one of the most widely used food additives, with uses in everything from soft drinks to cheese. A SIDS Initial Assessment Report (SIAR) for citric acid was presented at SIDS Initial Assessment Meeting (SIAM) 11 in January 2001 and its status was determined to be, "currently of low priority for further work."

B. Evaluation of "Read Down" Patterns

The "Read Down" patterns were considered among the four major data areas (physical-chemical properties, environmental fate and transport, ecotoxicity, and mammalian toxicity) for each of the 13 compounds. Complete data sets are available for the acetic, fumaric, malic and citric acids. Several of the salts of these acids also have relatively complete data sets. The category is characterized by

acids and their salts, all of which readily dissociate in solution. This dissociation is followed by relatively rapid biodegradation and/or utilization in living organisms. The available data suggest that the cationic portion of the salt (e.g., Ca^{2+}, Mg^{2+}, K^{+}, Na^{+}) does not significantly affect the relative toxicity of these compounds. Based on the similarities in structure and behavior, the widespread natural occurrence in many fruits and vegetables, and the long history of use as food additives, the Panel believes that no further testing is necessary to predict the environmental fate, ecotoxicity or mammalian toxicity of these compounds.

VII. SUMMARY OF ACETIC ACID AND SALTS CATEGORY

The 13 compounds in the category are acetic acid, its salts, and three structurally related acids (fumaric, malic, citric), as well as the salts of the citric acid. These compounds are grouped together because of their close structural relationships, their natural occurrence in plants and animals, and their fundamental role in cell metabolism, particularly in the tricarboxylic acid cycle (also known as the Citric Acid Cycle or Kreb's Cycle), which is where humans get their energy. These compounds are all carboxylic acids or their respective salts. They are all listed as GRAS by the USFDA and have widespread use as food additives.

The Panel believes the available information supports the following conclusions. All of these acids and salts are highly water soluble and have low to moderate volatility. They dissociate readily in solution and biodegrade rapidly or are utilized in the body. They are not persistent in the environment.

These compounds all exhibit relatively low toxicity to aquatic organisms, with any toxicity observed related to the effect of lowered pH. Likewise, these compounds all exhibit relatively low acute mammalian toxicity. Similarly, no significant effects were observed in genotoxicity, reproductive, and developmental/teratogenic testing.

VIII. CONCLUSIONS

The similarities in chemical structure and behavior of these 13 compounds, as well as the similarities found in the available testing data, support assessing these compounds under a single Acetic Acid and Salts category. The Panel believes that the available data sufficiently characterize the physical-chemical properties, environmental fate, ecotoxicity and mammalian toxicity of the group. Where reliable study data do not appear to exist, the missing values can be estimated using the available data of related chemicals within the group. In addition, these compounds have enjoyed widespread use as additives in a multitude of foods over many years. Therefore, based on the available data, the structural similarities, the natural occurrence, and the lack of significant toxicity, the Panel believes that no further testing is necessary to characterize the compounds included in this category. Support for this conclusion was provided in a review of the SIAR for citric acid at SIAM 11 in January 2001, where its status was determined to be, "currently of low priority for further work."

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APPENDIX 1

SUMMARY DATA TABLE FOR ACETIC ACID AND SALTS CATEGORY

U.S. HIGH PRODUCTION VOLUME (HPV) CHEMICAL CHALLENGE PROGRAM

ROBUST SUMMARIES

for

ACETIC ACID AND SALTS CATEGORY

Prepared by
American Chemistry Council
Acetic Acid and Salts Panel

June 28, 2001

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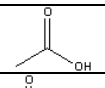
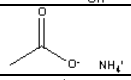
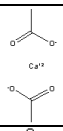
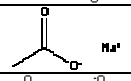
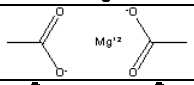
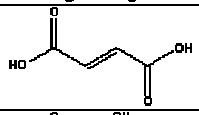
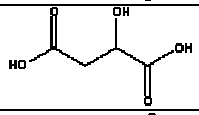
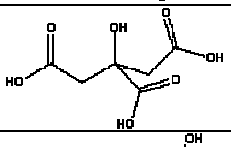
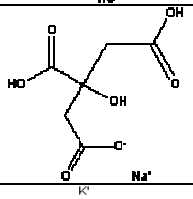
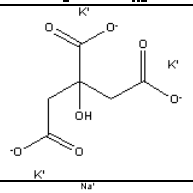
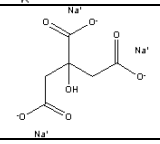
1. GENERAL SUBSTANCE INFORMATION

Robust summaries for the following substances are included in this Acetic Acid and Salts Category.

Chemical	CAS #	Structure
Acetic Acid	64-19-7	
Acetic Acid, Ammonium Salt	631-61-8	
Acetic Acid, Calcium Salt	62-54-4	
Acetic Acid, Potassium Salt	127-08-2	
Acetic Acid, Sodium Salt	127-09-3	
Acetic Acid, Magnesium Salt	142-72-3	
Acetic Acid, Manganese Salt	638-38-0	
Fumaric Acid	110-17-8	
Malic Acid	6915-15-7	
Citric Acid	77-92-9	
Citric Acid, Sodium Salt	994-36-5	
Citric Acid, Tripotassium Salt	866-84-2	
Citric Acid, Trisodium Salt	68-04-2	

2. PHYSICAL-CHEMICAL DATA

2.1 MELTING POINT

(a)

Value:	16.7 °C
Decomposition:	Yes [ ] No [ ] Ambiguous [X]
Sublimation:	Yes [ ] No [ ] Ambiguous [X]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid (64-19-7)
References:	Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(b)

Value:	114 °C
Decomposition:	Yes [ ] No [ ] Ambiguous [X]
Sublimation:	Yes [ ] No [ ] Ambiguous [X]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Ammonium Salt (631-61-8)
References:	Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(c)

Value:	80 °C
Decomposition:	Yes [ ] No [ ] Ambiguous [X]
Sublimation:	Yes [ ] No [ ] Ambiguous [X]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Magnesium Salt (142-72-3)
References:	Budavari, S. (ed.). 1996. Merck Index. 12th ed. Whitehouse Station: Merck Research Laboratories.

(d)

Value:	292 °C
Decomposition:	Yes [ ] No [ ] Ambiguous [X]
Sublimation:	Yes [ ] No [ ] Ambiguous [X]

Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]
Test substance: Acetic Acid, Potassium Salt (127-08-2)
References: Lewis, R.T. (ed.) 1994. Sax's Dangerous Properties of Industrial Materials. Eighth Edition. New York: Van Nostrand Reinhold Company.

(e)
Value: 58 °C
Decomposition: Yes [ ] No [ ] Ambiguous [X]
Sublimation: Yes [ ] No [ ] Ambiguous [X]
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]
Test substance: Acetic Acid, Sodium Salt (127-09-3)
References: Lewis, R.T. (ed.). 1994. Sax's Dangerous Properties of Industrial Materials. Eighth Edition. New York: Van Nostrand Reinhold Company.

(f)
Value: 287 °C
Decomposition: Yes [ ] No [ ] Ambiguous [X]
Sublimation: Yes [ ] No [ ] Ambiguous [X]
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]
Test substance: Fumaric Acid (110-17-8)
References: Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(g)
Value: 128 °C
Decomposition: Yes [ ] No [ ] Ambiguous [X]
Sublimation: Yes [ ] No [ ] Ambiguous [X]
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]
Test substance: Malic Acid (6915-15-7)
References: Lewis, R.T. (ed.). 1994. Sax's Dangerous Properties of Industrial Materials. Eighth Edition. New York: Van Nostrand Reinhold Company.

(h)

Value:	153 °C
Decomposition:	Yes [ ] No [ ] Ambiguous [X]
Sublimation:	Yes [ ] No [ ] Ambiguous [X]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid (77-92-9)
References:	Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(i)

Value:	211 °C
Decomposition:	Yes [ ] No [X] Ambiguous [ ]
Sublimation:	Yes [ ] No [X] Ambiguous [ ]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Calculated
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Citric Acid, Tripotassium Salt (866-84-2)
References:	Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(j)

Value:	150 °C
Decomposition:	Yes [X] No [ ] Ambiguous [ ]
Sublimation:	Yes [ ] No [X] Ambiguous [ ]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* OECD Guideline 102
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Citric Acid, Trisodium Salt (64-08-2)
Remarks:	Decomposition begins at 150°C with water loss.
References:	European Commission. 1996. Trisodium Citrate. International Uniform Chemical Information Database.

2.2 BOILING POINT

(a)

Value:	118.1 °C
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid (64-19-7)

References: Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(b)
Value: 160 °C
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]
Remarks: Substance decomposes above the reported value.
Test substance: Acetic Acid, Calcium Salt (62-54-4)
References: Budavari, S. (ed.). 1996. Merck Index. 12th ed. Whitehouse Station: Merck Research Laboratories.

(c)
Value: > 400 °C
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]
Remarks: Substance decomposes above the reported value.
Test substance: Acetic Acid, Sodium Salt (127-09-3)
References: Hoechst, A.G. 1993. Sicherheitsdatenblatt Natriumacetat entwaessert (04.03.1993). In European Commission. 1996. Sodium Acetate. International Uniform Chemical Information Database.

(d)
Value: 290 °C
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]
Remarks: Sublimes.
Test substance: Fumaric Acid (110-17-8)
References: Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(e)
Value: 140 °C
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]
Remarks: Substance decomposes above the reported value.
Test substance: Malic Acid (6915-15-7)

References: Lewis, R.T. (ed.). 1994. Sax's Dangerous Properties of Industrial Materials. Eighth Edition. New York: Van Nostrand Reinhold Company.

(f)
Value: Decomposes
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]
Test substance: Citric Acid (77-92-9)
References: Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(g)
Value: 230 °C
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]
Remarks: Substance decomposes when heated to the reported value.
Test substance: Citric Acid, Tripotassium Salt (866-84-2)
References: Lewis, R.T. (ed.). 1994. Sax's Dangerous Properties of Industrial Materials. Eighth Edition. New York: Van Nostrand Reinhold Company.

(h)
Value: Decomposes at red heat.
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]
Test substance: Citric Acid, Trisodium Salt (64-08-2)
References: Lewis, R.J., Sr. 1994. Hawley's Condensed Chemical Dictionary. 12th Ed. New York: Van Nostrand Reinhold Co.

2.4 VAPOUR PRESSURE

(a)
Value: 15.2 hPa (11.4 mm Hg)
Temperature: 20 °C
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]
Test substance: Acetic Acid (64-19-7)

References: Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(b)
Value: 1.9 x 10^{-4} hPa (1.4 x 10^{-4} mm Hg)
Temperature: 25 °C
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Calculated [X]; measured [ ]
GLP: Yes [ ] No [X] ? [ ]
Test substance: Acetic Acid, Ammonium Salt (631-61-8)
References: Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(c)
Value: 19.6 hPa (14.7 mm Hg)
Temperature: 25 °C
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Calculated [X]; measured [ ]
GLP: Yes [ ] No [X] ? [ ]
Test substance: Acetic Acid, Calcium Salt (62-54-4)
References: Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(d)
Value: 9.44 x 10^{-7} hPa (7.08 x 10^{-7} mm Hg)
Temperature: 25 °C
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Calculated [X]; measured [ ]
GLP: Yes [ ] No [X] ? [ ]
Test substance: Acetic Acid, Potassium Salt (127-08-2)
References: Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(e)
Value: 9.44 x 10^{-7} hPa (7.08 x 10^{-7} mm Hg)
Temperature: 25 °C
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Calculated [X]; measured [ ]
GLP: Yes [ ] No [X] ? [ ]
Test substance: Acetic Acid, Sodium Salt (127-09-3)

References: Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(f)
Value: 2.05×10^{-4} hPa (1.54×10^{-4} mm Hg)
Temperature: 25 °C
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]
Test substance: Fumaric Acid (110-17-8)
References: Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(g)
Value: 6.1×10^{-6} hPa (4.6×10^{-6} mm Hg)
Temperature: 25 °C
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Calculated [X]; measured [ ]
GLP: Yes [ ] No [X] ? [ ]
Test substance: Malic Acid (6915-15-7)
References: Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(h)
Value: 4.9×10^{-9} hPa (3.7×10^{-9} mm Hg)
Temperature: 25 °C
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Calculated [X]; measured [ ]
GLP: Yes [ ] No [X] ? [ ]
Test substance: Citric Acid (77-92-9)
References: Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(i)
Value: 2.79×10^{-12} hPa (2.09×10^{-12} mm Hg)
Temperature: 25 °C
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Calculated [X]; measured [ ]
GLP: Yes [ ] No [X] ? [ ]
Test substance: Citric Acid, Tripotassium Salt (866-84-2)
References: Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(j)

Value:	2.79 x 10^{-12} hPa (2.09 x 10^{-12} mm Hg)
Temperature:	25 °C
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Calculated [X]; measured [ ] GLP: Yes [ ] No [X] ? [ ]
Test substance:	Citric Acid, Trisodium Salt (64-08-2)
References:	Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

2.5 PARTITION COEFFICIENT logK_{ow}

(a)

Log Kow:	-0.17
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid (64-19-7)
References:	Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(b)

Log Kow:	-2.79
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Calculated [X]; measured [ ]
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Acetic Acid, Ammonium Salt (631-61-8)
References:	Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(c)

Log Kow:	-0.97
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Calculated [X]; measured [ ]
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Acetic Acid, Calcium Salt (62-54-4)
References:	Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(d)

Log Kow:	-3.72
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Calculated [X]; measured [ ]
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Acetic Acid, Potassium Salt (127-08-2)
References:	Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(e)

Log Kow:	-3.72
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Calculated [X]; measured [ ]
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Acetic Acid, Sodium Salt (127-09-3)
References:	Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(f)

Log Kow:	0.33
Temperature:	23 °C
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Fumaric Acid (110-17-8)
References:	Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(g)

Log Kow:	-1.26
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Malic Acid (6915-15-7)
References:	Hansch, C. and Leo, A. 1987. The Log P Database. Claremont, CA: Pomona College. In Hazardous Substances Databank (HSDB). Malic Acid. 1999. National Library of Medicine, Bethesda, MD.

(h)

Log Kow:	-1.72
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated

GLP: Yes [ ] No [ ] ? [X]
Test substance: Citric Acid (77-92-9)
References: Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(i)
Log Kow: -0.28
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Calculated [X]; measured [ ]
GLP: Yes [ ] No [X] ? [ ]
Test substance: Citric Acid, Tripotassium Salt (866-84-2)
References: Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(j)
Log Kow: -0.28
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Calculated [X]; measured [ ]
GLP: Yes [ ] No [X] ? [ ]
Test substance: Citric Acid, Trisodium Salt (64-08-2)
References: Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

2.6 WATER SOLUBILITY

A. Solubility

(a)
Value: 50 g/L
Temperature: 20 °C
Description: Miscible [ ]; Of very high solubility [ ]; Of high solubility [ ]; Soluble [X]; Slightly soluble [ ] Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]
Test substance: Acetic Acid (64-19-7)
References: Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(b)

Value:	1,480 g/L
Temperature:	4 °C
Description:	Miscible [ ]; Of very high solubility [X]; Of high solubility [ ]; Soluble [ ]; Slightly soluble [ ] Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Ammonium Salt (631-61-8)
References:	Lide, D.R. (ed). 1999. CRC Handbook of Chemistry and Physics. 80th Ed. Boca Raton: CRC Press.

(c)

Value:	430 g/L
Temperature:	25 °C
Description:	Miscible [ ]; Of very high solubility [X]; Of high solubility [ ]; Soluble [ ]; Slightly soluble [ ] Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Calcium Salt (62-54-4)
References:	Verdugt, B.V. 1992. Calcium acetate. Material Safety Data Sheet. In European Commission. 1996. Calcium Acetate. International Uniform Chemical Information Database.

(d)

Value:	Very soluble in water or alcohol
Description:	Miscible [ ]; Of very high solubility [ ]; Of high solubility [X]; Soluble [ ]; Slightly soluble [ ] Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Magnesium Salt (142-72-3)
References:	Budavari, S. (ed.). 1996. Merck Index. 12th ed. Whitehouse Station: Merck Research Laboratories.

(e)

Value:	Soluble in water or alcohol
Description:	Miscible [ ]; Of very high solubility [ ]; Of high solubility [ ]; Soluble [X]; Slightly soluble [ ] Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Manganese Salt (638-38-0)
References:	Budavari, S. (ed.). 1996. Merck Index. 12th ed. Whitehouse Station: Merck Research Laboratories.

(f)

Value:	2,530 g/L
Description:	Miscible [X]; Of very high solubility [ ]; Of high solubility [ ]; Soluble [ ]; Slightly soluble [ ] Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Potassium Salt (127-08-2)
References:	Lewis, R.T. (ed.). 1994. Sax's Dangerous Properties of Industrial Materials. Eighth Edition. New York: Van Nostrand Reinhold Company.

(g)

Value:	365 g/L
Temperature:	20 °C
Description:	Miscible [ ]; Of very high solubility [X]; Of high solubility [ ]; Soluble [ ]; Slightly soluble [ ] Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Sodium Salt (127-09-3)
References:	Hoechst, A.G. 1993. Sicherheitsdatenblatt Natriumacetat entwaessert (04.03.1993). In European Commission. 1996. Sodium Acetate. International Uniform Chemical Information Database.

(h)

Value:	7 g/L
Temperature:	25 °C

Description:	Miscible [ ]; Of very high solubility [ ]; Of high solubility [ ]; Soluble [X]; Slightly soluble [ ] Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Fumaric Acid (110-17-8)
References:	Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(i)

Value:	592 g/L
Temperature:	25 °C
Description:	Miscible [ ]; Of very high solubility [X]; Of high solubility [ ]; Soluble [ ]; Slightly soluble [ ] Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Malic Acid (6915-15-7)
References:	Yalkowsky, S.H. 1989. Arizona Database of Aqueous Solubilities. University of Arizona, College of Pharmacy. In Hazardous Substances Database (HSDB). Malic acid. 1999. National Library of Medicine, Bethesda, MD.

(j)

Value:	1,330 g/L
Temperature:	20 °C
Description:	Miscible [X]; Of very high solubility [ ]; Of high solubility [ ]; Soluble [ ]; Slightly soluble [ ] Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid (77-92-9)
References:	Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc

(k)

Value:	63 g/L

Description:	Miscible [ ]; Of very high solubility [ ]; Of high solubility [ ]; Soluble [X]; Slightly soluble [ ] Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Calculated
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Citric Acid, Tripotassium Salt (866-84-2)
References:	Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(l)

Value:	~425 g/L
Temperature:	25 °C
Description:	Miscible [ ]; Of very high solubility [ ]; Of high solubility [ ]; Soluble [X]; Slightly soluble [ ] Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid, Trisodium Salt (64-08-2)
References:	European Commission. 1996. Trisodium Citrate. International Uniform Chemical Information Database.

B. pH Value, pKa Value

(a)

pH Value:	2.5
Concentration:	50 g/L aqueous solution
Temperature:	20 °C
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
	(Where applicable, enter values for the dissociation constant(s) and the conditions under which they were measured.)
pKa value	4.76 at 25°C
Test substance:	Acetic Acid (64-19-7)
References:	Hoescht, A.G. 1994. Produktinformation Essigsaure der Abt. Marketing Chemikalien (04.03.1994) and Sicherheitsdatenblatt Essigsaure, reinst (18.04.1994). In European Commission. 1996. Acetic Acid. International Uniform Chemical Information Database. Serjeant, E.P. and Dempsey, B. 1979. Ionisation constants of organic acids in aqueous solution. IUPAC Chem. Data Ser. No. 23. In Hazardous Substances

Database (HSDB). 1999. Acetic Acid. National Library of Medicine, Bethesda, MD.

(b)

pH Value:	7. 0
Concentration:	390 g/L (5 M aqueous solution)
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
	(Where applicable, enter values for the dissociation constant(s) and the conditions under which they were measured).
Test substance:	Acetic Acid, Ammonium Salt (631-61-8)
References:	Budavari, S. (ed.). 1996. Merck Index. 12th ed. Whitehouse Station: Merck Research Laboratories.

(c)

pH Value:	7.6
Concentration:	32 g/L (0.2 M aqueous solution)
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
	(Where applicable, enter values for the dissociation constant(s) and the conditions under which they were measured.)
Test substance:	Acetic Acid, Calcium Salt (62-54-4)
References:	Budavari, S. (ed.). 1996. Merck Index. 12th ed. Whitehouse Station: Merck Research Laboratories.

(d)

pH Value:	9.7
Concentration:	98 g/L (1 M aqueous solution)
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
	(Where applicable, enter values for the dissociation constant(s) and the conditions under which they were measured.)
Test substance:	Acetic Acid, Potassium Salt (127-08-2)
References:	Budavari, S. (ed.). 1996. Merck Index. 12th ed. Whitehouse Station: Merck Research Laboratories.

(e)

pH Value:	7.5-9.0
Concentration:	50 g/L aqueous solution
Temperature:	20 °C

Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
	(Where applicable, enter values for the dissociation constant(s) and the conditions under which they were measured.)
Test substance:	Acetic acid, sodium salt (127-09-3)
References:	Hoechst, A.G. 1993. Sicherheitsdatenblatt Natriumacetat entwaessert (04.03.1993). In European Commission. 1996. Sodium acetate. International Uniform Chemical Information Database.

(f)

pH Value:	2.1
Concentration:	5 g/L aqueous solution
Temperature:	20 °C
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
	(Where applicable, enter values for the dissociation constant(s) and the conditions under which they were measured.)
pK1 value:	3.02 at 18°C
pK2:	4.46 at 18°C
Test substance:	Fumaric Acid (110-17-8)
References:	Weast, R.C. (ed.). 1989. Handbook of Chemistry and Physics. 69th Ed. Boca Raton: CRC Press. In Hazardous Substances Database (HSDB). 1999. Fumaric acid. National Library of Medicine, Bethesda, MD.

(g)

pK1 value:	3.40
pK2 value:	5.05
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Malic Acid (6915-15-7)
References:	Clayton, G.D. and Clayton, F.E. (eds.). 1994. Patty's Industrial Hygiene and Toxicology. 4th Ed. Volume II, Part E: Toxicology. John Wiley & Sons, Inc.

(h)

pH Value:	2.2
Concentration:	0.1 N aqueous solution
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated

GLP:	Yes [ ] No [ ] ? [X]
	(Where applicable, enter values for the dissociation constant(s) and the conditions under which they were measured.)
pK1 value:	3.13
pK2 value:	4.76
pK3 value:	6.40
Test substance:	Citric Acid (77-92-9)
References:	Budavari, S. (ed.). 1996. Merck Index. 12th ed. Whitehouse Station: Merck Research Laboratories.

(i)

pH Value:	~8
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]*
	Not stated
GLP:	Yes [ ] No [ ] ? [X]
	(Where applicable, enter values for the dissociation constant(s) and the conditions under which they were measured.)
Test substance:	Citric Acid, Trisodium Salt (64-08-2)
References:	Budavari, S. (ed.). 1996. Merck Index. 12th ed. Whitehouse Station: Merck Research Laboratories.

3. ENVIRONMENTAL FATE AND PATHWAYS

3.1 STABILITY

3.1.1 PHOTODEGRADATION

(a)

Type:	Air [X]; Water [ ]; Soil [ ]; Other [ ]
Light source:	Sunlight [ ]; Xenon lamp [ ]; Other [ ] Not stated
Indirect photolysis:	
Type of sensitizer:	OH
Concentration of sensitizer:	1,500,000 molecule/cm^3
Rate constant (radical):	5.1 x 10^{-13} cm^3/molecule*sec
Degradation:	~50% after 21 days
Method:	calculated [X]; measured [ ]
	[e.g. OECD, other(with the year of publication or updating of the method used)]
	Calculated by AOPWIN, Version 1.55, April 1994, Syracuse Research
GLP:	Yes [ ] No [X] ?[ ]
Test substance:	Acetic Acid (64-19-7)
Reliability:	Klimisch category 2

References:	Hoechst, A.G. 1994. Internal calculation. UCV (5.05.94). In European Commission. 1996. Acetic acid. International Uniform Chemical Information Database.

(b)

Type:	Air [ ]; Water [ ]; Soil [ ]; Other [X] Sorbed to silica gel
Light source:	Sunlight [ ]; Xenon lamp [X]; Other [ ]
Light spectrum:	290 nm
Spectrum of substance:	*[e.g. lambda (max.) (>295 nm) and epsilon (max.) or epsilon (295nm)]* >290 nm
Concentration of substance:	Not stated
Direct photolysis:	
Degradation:	6.6 % of applied amount after 17 hour exposure
Method:	calculated [ ]; measured [X] *[e.g. OECD, other(with the year of publication or updating of the method used)]* The test material was sorbed on silica gel and irradiated with light at 290 nm.
GLP:	Yes [ ] No [X] ?[ ]
Test substance:	Acetic Acid, Sodium Salt (127-09-3)
Reliability:	Klimisch category 2
References:	Freitag, D., Ballhorn, L. Geyer, H., and Korte, F. 1985. Environmental hazard profile of organic chemicals: An experimental method for the assessment of he behavior of organic chemicals in the ecosphere by means of simple laboratory tests with C14 labeled chemicals. Chemosphere 14(10):1589-1616.

(c)

Type:	Air [X]; Water [ ]; Soil [ ]; Other [ ]
Light source:	Sunlight [ ]; Xenon lamp [ ]; Other [ ] Not stated
Relative intensity:	Not stated
Indirect photolysis:	
Type of sensitizer:	OH
Concentration of sensitizer:	500,000 molecule/cm^3
Rate constant (radical):	5.3 x 10^{-12} cm^3/molecule*sec
Degradation:	50% after 7.3 hours
Method:	calculated [X]; measured [ ] *[e.g. OECD, other(with the year of publication or updating of the method used)]* Not stated
GLP:	Yes [ ] No [X] ?[ ]
Test substance:	Fumaric Acid (110-17-8)
Reliability:	Klimisch category 2
References:	Atkinson, R. 1987. A structure-activity relationship for the estimation of rate constants for the gas-phase reactions of OH radicals with organic compounds. J. Inter. Chem. Kinet. 19:799-828.

(d)

Type:	Air [X]; Water [ ]; Soil [ ]; Other [ ]
Indirect photolysis:	
Type of sensitizer:	OH
Concentration of sensitizer:	5 x 10^5 molecules/cm^3
Rate constant (radical):	7.76 x 10^{-12} cm^3/molecule*sec
Degradation:	Malic acid will degrade in the vapor phase by reaction with photochemically produced hydroxyl radicals at the stated rate, which corresponds to an atmospheric half-life of about 2 days.
Method:	*[e.g. OECD, other(with the year of publication or updating of the method used)]*
GLP:	Yes [ ] No [ ] ?[X]
Test substance:	Malic Acid (6915-15-7)
Reliability:	Klimisch category 2
References:	Meylan, W.M. and Howard, P.H. 1993. Chemosphere 26:2293-2299. In Hazardous Substances Database (HSDB). 1999. Malic acid. National Library of Medicine, Bethesda, MD.

3.1.2 STABILITY IN WATER

(a)

Remarks:	Acids dissociate in water.
Test substance:	Acetic Acid (64-19-7)

(b)

Remarks:	Salts dissociate in water.
Test substance:	Acetic Acid, Ammonium Salt (631-61-8)

(c)

Remarks:	Salts dissociate in water.
Test substance:	Acetic acid, calcium salt (62-54-4)

(d)

Remarks:	Salts dissociate in water.
Test substance:	Acetic acid, potassium salt (127-08-2)

(e)

Remarks:	Salts dissociate in water.
Test substance:	Acetic acid, sodium salt (127-09-3)

(f)

Type:	Abiotic (hydrolysis) [ ]; biotic (sediment) [ ]
Half life:	1-15 days in various natural waters
Method:	*[e.g. OECD, other(with the year of publication or updating of the method used)]* River die-away studies
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Fumaric Acid (110-17-8)

Remarks:	*(e.g. CAS number, name and percentage of degradation products)* Faster degradation occurred in more polluted waters. The degradation half life in distilled water was 55 days.
Reliability:	Klimisch category 2
References:	Saito, N. and Nagao, M. 1978. Okayama-Ken Kankyo Hoken Senta Nempo 2:274-276. In Hazardous Substances Database (HSDB). Fumaric acid. 1999. National Library of Medicine, Bethesda, MD.

(g)

Remarks:	When released into natural water, malic acid can be expected to biodegrade readily; as shown by a number of screening tests.
Test substance:	Malic Acid (6915-15-7)
Reliability:	Klimisch category 2
References:	Fournier, J.C, Hormatallah, A., Collu, T., and Froncek, B. 1992. Labelling of microbial biomass with radioactive substrates as a means to estimate pesticide effects in soil. Sci. Total Environ. 123/124:325-332.

(h)

Remarks:	Acids dissociate in water.
Test substance:	Citric Acid (77-92-9)

(i)

Remarks:	Salts dissociate in water.
Test substance:	Citric Acid, Sodium Salt (994-36-5)

(j)

Remarks:	Salts dissociate in water.
Test substance:	Citric Acid, Tripotassium Salt (866-84-2)

(k)

Remarks:	Salts dissociate in water.
Test substance:	Citric Acid, Trisodium Salt (64-08-2)

(l)

Remarks:	Salts dissociate in water.
Test substance:	Acetic acid, manganese salt (638-38-0)

(m)

Remarks:	Salts dissociate in water.
Test substance:	Acetic Acid, Magnesium Salt (142-72-3)

3.3 TRANSPORT AND DISTRIBUTION BETWEEN ENVIRONMENTAL COMPARTMENTS INCLUDING ESTIMATED ENVIRONMENTAL CONCENTRATIONS AND DISTRIBUTION PATHWAYS

Type:	Level I Fugacity Modeling
Temperature:	25 °C
Melting Point:	16.7 °C
Vapor Pressure:	1520 Pa (11.4 mm Hg)
Water Solubility:	50,000 g/m^3 (50 g/L)
Octanol-Water Partition:	0.676
Reaction Half-Lives:	Air: 21 days
	Water: 1 day
	Soil: 1 day
	Sediment: 1 day
Results:	Partitioning to:
	Air: 26.9 %
	Water: 73.1%
	Soil: 0.044%
	Sediment: 9.72 x 10^{-4} %
	Suspended Sediment: 3.04 x 10^{-5} %
	Fish: 2.47 x 10^{-6} %
Test Substance:	Acetic Acid (64-17-9)
Reliability:	Klimisch category 2
Reference:	Mackay 1991

Type:	Level I Fugacity Modeling
Temperature:	25 °C
Melting Point:	287 °C
Vapor Pressure:	0.0205 Pa (1.54 x 10^{-4} mm Hg)
Water Solubility:	7,000 g/m^3 (7 g/L)
Octanol-Water Partition:	2.138
Reaction Half-Lives:	Air: 0.3 days
	Water: 1 day
	Soil: 1 day
	Sediment: 1 day
Results:	Partitioning to:
	Air: 6.84 x 10^{-3} %
	Water: 99.8%
	Soil: 0.189%
	Sediment: 4.20 x 10^{-3} %
	Suspended Sediment: 1.31 x 10^{-4} %
	Fish: 1.07 x 10^{-5} %
Test Substance:	Fumaric Acid (110-17-8)
Reliability:	Klimisch category 2
Reference:	Mackay 1991

Type:	Level I Fugacity Modeling
Temperature:	25 °C
Melting Point:	128 °C
Vapor Pressure:	6.1×10^{-4} Pa (4.6×10^{-6} mm Hg)
Water Solubility:	592,000 g/m^3 (592 g/L)
Octanol-Water Partition:	0.055
Reaction Half-Lives:	Air: 2 days
	Water: 1 day
	Soil: 1 day
	Sediment: 1 day
Results:	Partitioning to:
	Air: 2.79×10^{-6} %
	Water: 100.0%
	Soil: 4.87×10^{-3} %
	Sediment: 1.08×10^{-4} %
	Suspended Sediment: 3.38×10^{-6} %
	Fish: 2.75×10^{-7} %
Test Substance:	Malic Acid (6915-15-7)
Reliability:	Klimisch category 2
Reference:	Mackay 1991

Type:	Level I Fugacity Modeling
Temperature:	25 °C
Melting Point:	153 °C
Vapor Pressure:	4.9×10^{-7} Pa (3.7×10^{-9} mm Hg)
Water Solubility:	1.33×10^{6} g/m^3 (1330 g/L)
Octanol-Water Partition:	0.019
Reaction Half-Lives:	Water: 1 day
	Soil: 1 day
	Sediment: 1 day
Results:	Partitioning to:
	Air: 1.43×10^{-9} %
	Water: 100.0%
	Soil: 1.69×10^{-3} %
	Sediment: 3.75×10^{-5} %
	Suspended Sediment: 1.17×10^{-6} %
	Fish: 9.53×10^{-8} %
Test Substance:	Citric Acid (77-92-9)
Reliability:	Klimisch category 2
Reference:	Mackay 1991

3.4 IDENTIFICATION OF MAIN MODE OF DEGRADABILITY IN ACTUAL USE

Remarks: See biodegradation

3.5 BIODEGRADATION

(a)

Type:	Aerobic [ ]; Anaerobic [X]
Inoculum:	Adapted [ ]; Non-adapted [X];
Concentration of the chemical:	30 mg-C/l related to COD [ ]; DOC [X]; Test substance [ ]
Medium:	Water [ ]; Water-sediment [ ]; Soil [ ]; Sewage treatment [X]
Degradation:	99 % reduction after 7 days
Results:	Readily biodeg. [X]; Inherently biodeg. [ ]; Under test condition no biodegradation observed [ ]; Other [ ]
Method:	*[e.g. OECD, others(with the year of publication or updating of the method used)]* Test procedures were carried out in an enclosed glove box with N_2 atmosphere. Oxygen-free water was used. The test period was 4 weeks at 37 °C and with pH adjusted to 7. Biodegradation was determined by analyzing the decrease of DOC.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic acid (64-17-9)
Reliability:	Klimisch category 2
References:	Kameya, T., Murayama, T., Urano, K., and Kitano, M. 1995. Biodegradation ranks of priority organic compounds under anaerobic conditions. Sci. Total Environ. 170(1-2):43-51.

(b)

Results:	Biodegrades in days to weeks.
Method:	*[e.g. OECD, others(with the year of publication or updating of the method used)]* Calculated.
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Acetic Acid, Ammonium Salt (631-61-8)
Reliability:	Klimisch category 2
References:	Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(c)

Type:	Aerobic [X]; Anaerobic [ ]
Medium:	Water [ ]; Water-sediment [ ]; Soil [ ]; Sewage treatment [X]
Results:	Readily biodeg. [X]; Inherently biodeg. [ ]; Under test condition no biodegradation observed [ ]; Other [ ]
Method:	*[e.g. OECD, others(with the year of publication or updating of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic acid, calcium salt (62-54-4)

Remarks:	Activated sludge, industrial
Reliability:	Klimisch category 4
References:	European Commission. 1996. Calcium acetate. International Uniform Chemical Information Database.

(d)

Type:	Aerobic [X]; Anaerobic [ ]
Inoculum:	Adapted [ ]; Non-adapted [X]; activated sludge
Concentration of the chemical:	160 mg/L related to COD [ ]; DOC [ ]; Test substance [X]
Medium:	Water [ ]; Water-sediment [ ]; Soil [ ]; Sewage treatment [X]
Degradation:	100 % reduction after 5 days
Results:	Readily biodeg. [ ]; Inherently biodeg. [X]; Under test condition no biodegradation observed [ ]; Other [ ]
Method:	*[e.g. OECD, others(with the year of publication or updating of the method used)]* OECD Guideline 302B (1981) "Inherent biodegradability: Modified Zahn-Wellens Test"
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Acetic Acid, Sodium Salt (127-09-3)
Reliability:	Klimisch category 2
References:	Huels study (unpublished). In European Commission. 1996. Sodium acetate. International Uniform Chemical Information Database.

(e)

Type:	Aerobic [X]; Anaerobic [ ]
Inoculum:	Adapted [ ]; Non-adapted [X];
Concentration of the chemical:	0.05 mg/L related to COD [ ]; DOC [ ]; Test substance [X]
Medium:	Water [ ]; Water-sediment [ ]; Soil [ ]; Sewage treatment [X]
Degradation:	52.6 % reduction after 5 days
Results:	Readily biodeg. [ ]; Inherently biodeg. [X]; Under test condition no biodegradation observed [ ]; Other [ ]
Method:	*[e.g. OECD, others(with the year of publication or updating of the method used)]* Batch-Test; mineralization related to maximum theoretical CO_2-production; measurement of 14 CO_2; Temperature was maintained at 25 ± 2 °C.
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Acetic Acid, Sodium Salt (127-09-3)
Reliability:	Klimisch category 2
References:	Freitag, D., Ballhorn, L., Geyer, H., and Korte, F. 1985. Environmental hazard profile of organic chemicals: An experimental method for the assessment of he behavior of organic chemicals in the ecosphere by means of simple laboratory tests with C14 labeled chemicals. Chemosphere 14(10):1589-1616.

(f)

Type:	Aerobic [X]; Anaerobic [ ]
Inoculum:	Adapted [ ]; Non-adapted [X]; predominantly domestic sewage
Concentration of the chemical:	10 mg/L related to COD [ ]; DOC [X]; Test substance [ ]
Medium:	Water [ ]; Water-sediment [ ]; Soil [ ]; Sewage treatment [X]
Degradation:	98 % reduction after 21 days
Results:	Readily biodeg. [X]; Inherently biodeg. [ ]; Under test condition no biodegradation observed [ ]; Other [ ]
Method:	*[e.g. OECD, others(with the year of publication or updating of the method used)]* OECD Guideline 301 E (1981) "Ready biodegradability: Modified OECD Screening Test"
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Fumaric Acid (110-17-8)
Reliability:	Klimisch category 2
References:	Huels, A.G. 1992. Unpublished results dated 3/4/92. In European Commission. 1996. Fumaric acid. International Uniform Chemical Information Database.

(g)

Type:	Aerobic [X]; Anaerobic [ ]
Inoculum:	Adapted [ ]; Non-adapted [X]; domestic sewage
Concentration of the chemical:	600 mg/L related to COD [ ]; DOC [ ]; Test substance [X]
Medium:	Water [ ]; Water-sediment [ ]; Soil [ ]; Sewage treatment [X]
Degradation:	98 % reduction after 48 hours
Results:	Readily biodeg. [X]; Inherently biodeg. [ ]; Under test condition no biodegradation observed [ ]; Other [ ]
Kinetics:	0% in 0 hours 34% in 18 hours 84% in 24 hours 97% in 40 hours 98% in 48 hours
Method:	*[e.g. OECD, others(with the year of publication or updating of the method used)]* OECD Guideline 302 B (1994)"Inherent biodegradability: Modified Zahn-Wellens Test"
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	Citric Acid (77-92-9)
Reliability:	Klimisch category 2
References:	European Commission. 1996. Citric acid. International Uniform Chemical Information Database.

(h)

Type:	Aerobic [X]; Anaerobic [ ]
Inoculum:	Adapted [ ]; Non-adapted [ ]; effluent from domestic sewage treatment plant

Concentration of the chemical:	5 mg/L related to COD [ ]; DOC [ ]; Test substance [X]
Medium:	Water [ ]; Water-sediment [ ]; Soil [ ]; Sewage treatment [X]
Degradation:	90 % reduction after 30 days
Results:	Readily biodeg. [X]; Inherently biodeg. [ ]; Under test condition no biodegradation observed [ ]; Other [ ]
Method:	*[e.g. OECD, others(with the year of publication or updating of the method used)]*
GLP:	Yes [ ] No [X] ? [ ] Directive 84/449/EEC, C.6 "Biotic degradation – closed bottle test"
Test substance:	Citric Acid, Trisodium Salt (64-08-2)
Reliability:	Klimisch category 2
References:	European Commission. 1996. Trisodium citrate. International Uniform Chemical Information Database.

3.7 BIOACCUMULATION

Remarks:	Does not bioaccumulate because these acids and their salts dissociate and biodegrade rapidly.

4. ECOTOXICITY

4.1 ACUTE/PROLONGED TOXICITY TO FISH

(a)

Type of test:	Static [ ]; Semi-static [ ]; Flow-through [ ]; Other *(e.g. field test)* [ ]; Not stated
Species:	*Lepomis macrochirus* (Bluegill sunfish)
Exposure period:	96 hours
Results:	LC_{50} (96 h) = 75 mg/L
Analytical monitoring:	Yes [ ]; No [ ]; ? [X]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid (64-19-7)
Remarks:	Data from unknown literature source as cited by Price.
Reliability:	Klimisch category 2
References:	Price, K.S., Waggy, G.T., and Conway, R.A. 1974. Brine shrimp bioassay and seawater BOD of petrochemicals. J. Water Pollut Control Fed. 46(1):63-77.

(b)

Type of test:	Static [X]; Semi-static [ ]; Flow-through [ ]; Other *(e.g. field test)* [ ]; Not stated
Species:	*Gambusia affinis* (Mosquito fish)
Exposure period:	96 hours
Results:	LC_{50} (96 h) = 251 mg/L
Analytical monitoring:	Yes [ ]; No [ ]; ? [X]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Test water was maintained at pH 6.9 – 8.7 and 16-25°C
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid (64-19-7)
Remarks:	Test data from original citation.
Reliability:	Klimisch category 2
References:	Wallen I.E., Greer, W.C., and Lasater, R. 1957. Toxicity to *Gambusia affinis* of certain pure chemicals in turbid waters. Sewage Ind. Wastes 23(6):695-711.

(c)

Type of test:	Static [X]; Semi-static [ ]; Flow-through [ ]; Other *(e.g. field test)* [ ]; Not stated
Species:	*Pimephales promelas* (Fathead minnow)
Exposure period:	96 hours
Results:	LC_{50} (96 h) = 79-88 mg/L
Analytical monitoring:	Yes [ ]; No [ ]; ? [X]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Fathead minnows were exposed under static conditions to a series of concentrations of ammonium acetate.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Ammonium Salt (631-61-8)
Reliability:	Klimisch category 2
References:	Mattson, V.R., Arthur, J.W., and Walbridge, C.A. 1976. Acute toxicity of selected organic compounds to fathead minnows. Ecol. Res. Ser. EPA-600/3-76-097, Environ. Res. Lab., USEPA, Duluth, MN: 12p.

(d)

Type of test:	Static [ ]; Semi-static [ ]; Flow-through [ ]; Other *(e.g. field test)* [ ]; Not stated
Species:	*Gambusia affinis* (Mosquito fish)
Exposure period:	96 hours
Results:	LC_{50} (96 h) = 238 mg/L
Analytical monitoring:	Yes [ ]; No [ ]; ? [X]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Ammonium Salt (631-61-8)
Reliability:	Klimisch category 4

References: Jones, H.R. 1971. Environmental control in the organic and petrochemical industries. Noyes Data Corporation. In Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(e)

Type of test: Static [ ]; Semi-static [X]; Flow-through [ ]; Other *(e.g. field test)* [ ]

Species: *Salmo gairdneri* (Rainbow trout)

Exposure period: 96 hours

Results: LC_{50} (96 h) = 6,100 mg/L

Analytical monitoring: Yes [ ]; No [X]; ? [ ]

Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
OECD Guideline 203

GLP: Yes [ ] No [ ] ? [X]

Test substance: Acetic acid, potassium salt (127-08-2)

Remarks: Test used a commercial formulation.

Reliability: Klimisch category 2

References: Huntingdon Research Centre. 1992. Report No. BPC142/911702. In European Commission. 1996. Potassium acetate. International Uniform Chemical Information Database.

(f)

Type of test: Static [ ]; Semi-static [X]; Flow-through [ ]; Other *(e.g. field test)* [ ]

Species: *Brachydanio rerio* (Zebra fish)

Exposure period: 96 hours

Results: LC_{50} (96 h) >100 mg/L

Analytical monitoring: Yes [X]; No [ ]; ? [ ]

Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Directive 92/69/EEC, C.1 (1992)

GLP: Yes [X] No [ ] ? [ ]

Test substance: Acetic Acid, Sodium Salt (127-09-3)

Remarks: Concentration refers to waterfree substance. No mortality was observed at the highest concentration tested.

Reliability: Klimisch category 2

References: Huels. 1993. Report No. FK 1241 (unpublished). In European Commission. 1996. Sodium acetate. International Uniform Chemical Information Database.

(g)

Type of test: Static [X]; Semi-static [ ]; Flow-through [ ]; Other *(e.g. field test)* [ ]

Species: *Pimephales promelas* (Fathead minnow)

Exposure period: 120 hours

Results: LC_{50} (96 h) = 13.3 mg/L

Analytical monitoring:	Yes [ ]; No [ ]; ? [X]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Fathead minnow embryos were exposed to increasing concentrations of acetic acid sodium salt for 5 days under static conditions.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Sodium Salt (127-09-3)
Remarks:	95% confidence intervals were 12.43 and 14.31 mg/L.
Reliability:	Klimisch category 2
References:	DeYoung, D.J., Bantle, J.A., Hull, M.A., and Burks, S.L. 1996. Differences in sensitivity to developmental toxicants as seen in *Xenopus* and *Pimephales* embryos. Bull. Environ. Contam. Toxicol. 56:143-150.

(h)

Type of test:	Static [X]; Semi-static [ ]; Flow-through [ ]; Other *(e.g. field test)* [ ]
Species:	*Brachydanio rerio* (Zebra fish)
Exposure period:	48 hours
Results:	LC_{50} (48 h) = 245 mg/L
Analytical monitoring:	Yes [ ]; No [X]; ? [ ]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* DIN 38412 Part 15
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Fumaric Acid (110-17-8)
Reliability:	Klimisch category 2
References:	Huels Ag: AIDA – Grunddatensatz, date of last update 0.4.03.92. In European Commission. 1996. Fumaric acid. International Uniform Chemical Information Database.

(i)

Type of test:	Static [X]; Semi-static [ ]; Flow-through [ ]; Other *(e.g. field test)* [ ]
Species:	*Lepomis macrochirus* (Bluegill sunfish)
Exposure period:	96 hours
Results:	LC_{50} (96 h) = 1,516 mg/L
Analytical monitoring:	Yes [ ]; No [ ]; ? [X]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid (77-92-9)
Reliability:	Klimisch category 4
References:	Schwartz and Davis. 1973. United States Environmental Protection Agency (USEPA). EPA-600/2-74-003. In European Commission. 1996. Citric acid. International Uniform Chemical Information Database.

(j)

Type of test:	Static [ ]; Semi-static [ ]; Flow-through [ ]; Other *(e.g. field test)* [ ]; Not stated
Species:	*Poecilia reticulata* (Guppy)
Exposure period:	96 hours
Results:	LC_{50} (96 h) >18,000-32,000 mg/L
Analytical monitoring:	Yes [X]; No [ ]; ? [ ]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid, Trisodium Salt (64-08-2)
Remarks:	The same result was obtained in a study on *Oryzias latipes* (medaka).
Reliability:	Klimisch category 4
References:	Sloof, W. and Kappers, F.I. 1982. Rijksinstituut voor drinkwatervoorziening (RID) Nr. 82-4. In European Commission. 1996. Trisodium citrate. International Uniform Chemical Information Database.

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

A. *Daphnia*

(a)

Type of test:	Static [X]; Semi-static [ ]; flow-through [ ]; Other *(e.g. field test)* [ ];
Species:	*Daphnia magna*
Exposure period:	24 hours
Results:	LC_{50} = 47 mg/L
Analytical monitoring:	Yes [ ]; No [ ]; ? [X]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid (64-19-7)
Remarks:	Based on the results reported in Bringmann and Kuhn 1982 (see next summary for reference), this value is likely attributed to the low pH of the system.
Reliability:	Klimisch category 2

References:	Elkins, H.F., et al. 1956. Sewage Ind. Wastes 28(12): 1475. In Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.
(b)	
Type of test:	Static [X]; Semi-static [ ]; flow-through [ ]; Other [ ]
Species:	*Daphnia magna*
Exposure period:	24 hours
Results:	EC_{50} = 6,000 mg/L
Analytical monitoring:	Yes [ ]; No [ ]; ? [X]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* The stock cultures of test organisms were fed dry algae, but no feeding occurred during the 24-hour exposure. The testing took place in a defined standardized culture medium (artificial fresh water). The endpoint was immobilization.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid (64-19-7)
Remarks:	The stated result was for test solutions neutralized (pH 8.0) prior to daphnid exposures. For the un-neutralized test, the 24-hour EC_{50} was 95 mg/L. The pH of un-neutralized test solutions was not stated.
Reliability:	Klimisch category 2
References:	Bringmann, V. G. and Kuhn, R. 1982. Results of toxic action of water pollutants on *Daphnia magna strauss* tested by an improved standardized procedure. Z. Wasser Abwasser Forsch. 15(1):1-6.
(c)	
Type of test:	Static [X]; Semi-static [ ]; flow-through [ ]; Other [ ]
Species:	*Daphnia magna*
Exposure period:	48 hours
Results:	EC_{50} = 65 mg/L
Analytical monitoring:	Yes [ ]; No [ ]; ? [X]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* *Daphnia magna* were exposed to a series of concentrations of acetic acid. The endpoint was immobilization.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid (64-19-7)
Remarks:	Test solutions were apparently un-neutralized.
Reliability:	Klimisch category 2
References:	Janssen, C.R., Espiritu, E.Q., and Persoone, G. 1993. Evaluation of the new "Enzymatic Inhibition" criterion for rapid toxicity testing with *Daphnia magna*. In: Soares, A. and Calow, P. (Eds.), Progress in Standardization of Aquatic Toxicity Tests. Lewis Publishers, New York, pp. 71-81.

(d)

Type of test:	Static [X]; Semi-static [ ]; flow-through [ ]; Other *(e.g. field test)* [ ]; Not stated
Species:	*Daphnia magna*
Exposure period:	24 hours
Results:	LC_{50} = 7,170 mg/L
Analytical monitoring:	Yes [ ]; No [ ]; ? [X]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Sodium Salt (127-09-3)
Remarks:	Was summarized in the Potassium acetate IUCLID Data Sheet but indicated the test substance was acetic acid, sodium salt.
Reliability:	Klimisch category 4
References:	Bringmann and Kuhn. 1977. Z. Wasser Abwasser Forschung 10(5):161-166. In European Commission. 1996. Potassium acetate. International Uniform Chemical Information Database.

(e)

Type of test:	Static [X]; Semi-static [ ]; flow-through [ ]; Other *(e.g. field test)* [ ]; Not stated
Species:	*Daphnia magna*
Exposure period:	48 hours
Results:	EC_{50} > 1,000 mg/L
Analytical monitoring:	Yes [ ]; No [X]; ? [ ]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Directive 84/449/EEC, C.2
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	Acetic Acid, Sodium Salt (127-09-3)
Reliability:	Klimisch category 2
References:	Huels. 1993. Report No. FK 1241 (unpublished). In European Commission. 1996. Sodium acetate. International Uniform Chemical Information Database.

(f)

Type of test:	Static [X]; Semi-static [ ]; flow-through [ ]; Other *(e.g. field test)* [ ]
Species:	*Daphnia magna*
Exposure period:	48 hours EC_{50} = 212 mg/L
Analytical monitoring:	Yes [ ]; No [X]; ? [ ]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* First instar *Daphnia* (< 24 hrs old) were used for all tests. Method as described in EPA-660/3-75-009.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Fumaric Acid (110-17-8)

Remarks:	Endpoint was immobilization.
Reliability:	Klimisch category 2
References:	Randall, T.L. and Knopp, P.V. 1980. Detoxification of specific organic substances by wet oxidation. J. Water Pollut. Control Fed. 52(8):2117-2130. United States Environmental Protection Agency (USEPA). 1975. Methods for acute toxicity tests with fish, macroinvertebrates, and amphibians. Ecological Research Series, EPA-660/3-75-009.

(g)

Type of test:	Static [X]; Semi-static [ ]; flow-through [ ]; Other *(e.g. field test)* [ ]
Species:	*Daphnia magna*
Exposure period:	48 hours
Results:	LC_{50} = 240 mg/L
Analytical monitoring:	Yes [ ]; No [X]; ? [ ]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Fifteen daphnids (≤24-hours old, first instar) were exposed to concentrations of 100, 180, 320, 560 and 1,000 mg/L, along with a control group. Test temperature remained constant at 20 °C throughout the study.
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	Malic Acid (6915-15-7)
Remarks:	Mortality and/or surfacing was observed in test concentrations ≥180 mg/L. Low pH (3.2-4.5) caused by the acidic test material may be considered the primary cause of the observed toxicity.
Reliability:	Klimisch category 1
References:	ABC Laboratories. 1989. Acute freshwater invertebrate toxicity study – malic acid. Report # 37763. Prepared for Proctor & Gamble.

(h)

Type of test:	Static [X]; Semi-static [ ]; flow-through [ ]; Other *(e.g. field test)* [ ]; Not stated
Species:	*Daphnia magna*
Exposure period:	24 hours
Results:	EC_{50} = 1,535 mg/L
Analytical monitoring:	Yes [ ]; No [ ]; ? [X]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* The stock cultures of test organisms were fed dry algae, but no feeding occurred during the 24-hour exposure. The testing took place in a defined standardized culture medium (artificial fresh water). The endpoint was immobilization.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid (77-92-9)

Reliability:	Klimisch category 2
References:	Bringmann, V. G. and Kuhn, R. 1982. Results of toxic action of water pollutants on *Daphnia magna strauss* tested by an improved standardized procedure. Z. Wasser Abwasser Forsch. 15(1):1-6.

(i)

Type of test:	Static [X]; Semi-static [ ]; flow-through [ ]; Other *(e.g. field test)* [ ]; Not stated
Species:	*Daphnia magna*
Exposure period:	72 hours
Results:	EC_{50} = 120 mg/L
Analytical monitoring:	Yes [ ]; No [ ]; ? [X]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid (77-92-9)
Reliability:	Klimisch category 4
References:	Ellis, M.M. 1937. Bull. Bur. Fish 48:365. In European Commission. 1996. Citric acid. International Uniform Chemical Information Database.

(j)

Type of test:	Static [X]; Semi-static [ ]; flow-through [ ]; Other *(e.g. field test)* [ ]; Not stated
Species:	*Daphnia magna*
Exposure period:	48 hours
Results:	EC_{50} = 5,600 – 10,000 mg/L
Analytical monitoring:	Yes [ ]; No [ ]; ? [X]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid, Trisodium Salt (64-08-2), purity: 50%
Reliability:	Klimisch category 4
References:	Sloof, W. and Kappers, F.I. 1982. Rijksinstituut voor drinkwatervoorziening (RID) Nr. 82-4. In European Commission. 1996. Trisodium citrate. International Uniform Chemical Information Database.

4.3 TOXICITY TO AQUATIC PLANTS, e.g. algae

(a)

Species:	*Scenedesmus quadricauda* (algae)
Endpoint:	Biomass [ ]; Growth rate [ ]; Other [X](Growth inhibition)
Exposure period:	8 days
Results:	TT (toxicity threshold) = 4,000 mg/L

Analytical monitoring:	Yes [ ]; No [ ]; ? [X]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Filled culture tubes were maintained at 27 °C and relative humidity of 50%. The concentration of the algal suspension is measured turbidmetrically (while diffused light is screened off) and expressed by the extinction of the primary light of the monochromatic radiation at 578 nm for a layer of 10 mm thickness.
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Acetic Acid (64-19-7)
Remarks:	Toxicity threshold is defined as the pollutant concentration resulting in a mean extinction value that is ≥ 3% below the mean of the extinction value for the non-toxic dilutions of the test culture.
Reliability:	Klimisch category 2
References:	Bringmann, G. and Kuhn, R. 1980. Comparison of the toxicity thresholds of water pollutants to bacteria, algae, and protozoa in the cell multiplication inhibition test. Water Res. 14:231-241.

(b)

Species:	*Anacystis nidulans* (Cyanobacterium)
Endpoint:	Biomass [ ]; Growth rate [X]; Other [ ]
Exposure period:	60 hours
Results:	Growth inhibition in photoautotrophic algae at 2,460 mg/L (0.03 mol/L) after 60 hours.
Analytical monitoring:	Yes [ ]; No [ ]; ? [X]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* A static test was conducted at a temperature of 30°C, a pH of 7.6-7.8, and a light intensity of 1,000 ft. candles. Growth rate was determined by measuring optical density of the cultures.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Sodium Salt (127-09-3)
Remarks:	Retardation of growth (i.e., slowed but did not otherwise restrict growth) occurred at 820 and 1,640 mg/L (0.01 and 0.02 mol/L). Inhibition of growth (i.e., prevented growth) occurred at 2,460 and 3,290 mg/L (0.03 and 0.04 mol/L). However, even at the highest concentrations, the cultures remained viable after being transferred to clean culture water.
Reliability:	Klimisch category 2
References:	Hoare, D.S. et al. 1967. J. Gen. Microbiol. 49:351-370. In European Commission. 1996. Sodium Acetate. International Uniform Chemical Information Database.

(c)

Species:	*Scenedesmus subspicatus* (Algae)
Endpoint:	Biomass [ ]; Growth rate [X]; Other [ ]

Exposure period:	72 hours
Results:	EC_{10} (72 h) = 32 mg/L EC_{50} (72 h) = 41 mg/L CE_{90} (72 h) = 49 mg/L
Analytical monitoring:	Yes [ ]; No [X]; ? [ ]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* UBA algal growth inhibition test (proposed method February 1984)
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Fumaric Acid (110-17-8)
Reliability:	Klimisch category 2
References:	AIDA – Huels AG Report No. AW 1501. 1988. Not published. In European Commission. 1996. Fumaric Acid. International Uniform Chemical Information Database.

(d)

Species:	*Scenedesmus quadricauda* (algae)
Endpoint:	Biomass [ ]; Growth rate [ ]; Other [X](Growth inhibition)
Exposure period:	8 days
Results:	TT (toxicity threshold) = 640 mg/L
Analytical monitoring:	Yes [ ]; No [ ]; ? [X]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Filled culture tubes were maintained at 27 °C and relative humidity of 50%. The concentration of the algal suspension is measured turbidmetrically (while diffused light is screened off) and expressed by the extinction of the primary light of the monochromatic radiation at 578 nm for a layer of 10 mm thickness.
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Citric Acid (77-92-9)
Remarks:	Toxicity threshold is defined as the pollutant concentration resulting in a mean extinction value that is ≥ 3% below the mean of the extinction value for the non-toxic dilutions of the test culture.
Reliability:	Klimisch category 2
References:	Bringmann, G. and Kuhn, R. 1980. Comparison of the toxicity thresholds of water pollutants to bacteria, algae, and protozoa in the cell multiplication inhibition test. Water Res. 14:231-241.

(e)

Species:	*Chlorella vulgaris*
Endpoint:	Biomass [X]; Growth rate [ ]; Other [ ]
Exposure period:	96 hours
Results:	EC_{50} > 18,000 – 32,000 mg/L
Analytical monitoring:	Yes [X]; No [ ]; ? [ ]

Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* OECD Guideline 201 (1982) "Algae, Growth Inhibition Test"
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid, Trisodium Salt (64-08-2); purity: 50% solution
Reliability:	Klimisch category 2
References:	Sloof, W. and Kappers, F.I. 1982. Rijksinstituut voor drinkwatervoorziening (RID) Nr. 82-4. In European Commission. 1996. Trisodium citrate. International Uniform Chemical Information Database.

5. TOXICITY

5.1 ACUTE TOXICITY

5.1.1 ACUTE ORAL TOXICITY

(a)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Mouse
Value:	4960 mg/kg b.w.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid (64-19-7)
Reliability:	Klimisch category 4
References:	Woodward, G., Lang, S.R., Nelson, K.W., and Calvery, H.O. 1941. J. Ind. Hyg. Toxicol. 23:78-82. In Clayton, G.D. and Clayton, F.E. (eds.). 1994. Patty's Industrial Hygiene and Toxicology. Volume II, Part E. Toxicology. New York: John Wiley & Sons, Inc.

(b)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Rat
Value:	4,280 mg/kg b.w.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Rats were given a single oral dose of 200,000 mg/L (0.200 g/ml) of acetic acid, calcium salt in water via intubation. A range-finding toxicity test was conducted as described in Smyth et al. 1962.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Calcium Salt (62-54-4)
Reliability:	Klimisch category 2

References: Smyth, H.F., Jr., Carpenter, C.P., Weil, C.S., Pozzani, U.C., Striegel, J.A., and Nycum, J.S. 1969. Range-finding toxicity data: List VII. Am. Ind. Hyg. Assoc. J. 30:470-476.
Smyth, H.F. Jr., Carpenter, C.P., Weil, C.S., Pozzani,, U.C., and Striegel, J.A. 1962. Range-finding toxicity data: List VI. Amer. Ind. Hyg. Assoc. J. 23:95-207.

(c)
Type: LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain: Rat
Value: 3,250 mg/kg b.w.
Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
Rats were given a single oral dose of 100,000 mg/L (0.100 g/ml) of acetic acid, potassium salt in water via intubation. A range-finding toxicity test was conducted as described in Smyth et al. 1962.
GLP: Yes [ ] No [ ] ? [X]
Test substance: Acetic Acid, Potassium Salt (127-08-2)
Reliability: Klimisch category 2
References: Smyth, H.F., Jr., Carpenter, C.P., Weil, C.S., Pozzani, U.C., Striegel, J.A., and Nycum, J.S. 1969. Range-finding toxicity data: List VII. Am. Ind. Hyg. Assoc. J. 30:470-476.
Smyth, H.F. Jr., Carpenter, C.P., Weil, C.S., Pozzani, U.C., and Striegel, J.A. 1962. Range-finding toxicity data: List VI. Amer. Ind. Hyg. Assoc. J. 23:95-207.

(d)
Type: LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain: Rat
Value: 3,530 mg/kg b.w.
Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]
Test substance: Acetic Acid, Sodium Salt (127-09-3)
Reliability: Klimisch category 2
References: Food and Agriculture Organization of the United Nations, Report Series. 40,127,67. In Lewis, R.T. (ed.). 1994. Sax's Dangerous Properties of Industrial Materials. Eighth Edition. New York: Van Nostrand Reinhold Company.

(e)
Type: LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain: Rat
Value: 10,700 mg/kg b.w. (male rats)
9,300 mg/kg b.w. (female rats)

Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Rats were given a single oral dose. Range finding toxicity test as described in Smyth et al. 1962.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Fumaric Acid (110-17-8)
Reliability:	Klimisch category 2
References:	Vernot, E.H., MacEwen, J.D., Haun, C.C., and Kinkead, E.R. 1977. Acute toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. Toxicol. Appl. Pharmacol. 42:417-423. Smyth, H.F. Jr., Carpenter, C.P., Weil, C.S., Pozzani, U.C., and Striegel, J.A. 1962. A range-finding toxicity data: List VI. Amer. Ind. Hyg. Assoc. J. 23:95-207.

(f)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Rat
Value:	10,000 mg/kg b.w.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Fumaric Acid (110-17-8)
Reliability:	Klimisch category 4
References:	Ullmann's Encyclopedia of Industrial Chemistry. 5^{th} Ed. Volume A16. In European Commission. 1996. Fumaric acid. International Uniform Chemical Information Database.

(g)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Mouse, Rat
Value:	1,600 – 3,200 mg/kg b.w.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Malic Acid (6915-15-7)
Reliability:	Klimisch category 2
References:	Eastman Kodak. 1981. Health Safety and Human Factors Laboratory, Rochester, New York. In BIBRA. 1992. Toxicology profile: Malic acid and its common salts. BIBRA International.

(h)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Rat (Sprague-Dawley)
Value:	11,700 mg/kg b.w.

Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Six 5-week old male SD-JCL rats weighing 110-140 g were used at each dosage group. A single oral dose was administered for each of a series of concentrations in volumes of 2 ml/100 g body weight. Behavior and mortality were observed for 7 days.
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Citric Acid (77-92-9), purity: 99.8% citric acid monohydrate
Remarks:	Observed effects at the higher concentration included motor ataxia, decreases in respiration and heart beat, and respiratory failure.
Reliability:	Klimisch category 2
References:	Yokotani, H., Usui, T., Nakaguchi, T., Kanabayashi, T. Tanda, M., and Aramaki, Y. 1971. Acute and subacute toxicological studies of TAKEDA-citric acid in mice and rats. J. Takeda Res. Lab. 30(1):25-31.

(i)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Mouse (1 CR)
Value:	5,790 mg/kg b.w.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Six 4-week old male ICR-JCL mice weighing 20-24 g were used at each dosage group. A single oral dose was administered for each of a series of concentrations in volumes of 0.5 ml/10 g b.w. Behavior and mortality were observed for 7 days.
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Citric Acid (77-92-9), purity : 99.8% citric acid monohydrate
Remarks:	Observed effects at the higher concentration included motor ataxia, decreases in respiration and heart beat, and respiratory failure.
Reliability:	Klimisch category 2
References:	Yokotani, H., Usui, T., Nakaguchi, T., Kanabayashi, T. Tanda, M., and Aramaki, Y. 1971. Acute and subacute toxicological studies of TAKEDA-citric acid in mice and rats. J. Takeda Res. Lab. 30(1):25-31.

(j)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Mouse
Value:	7,100 mg/kg b.w.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid, Sodium Salt (994-36-5)

Reliability:	Klimisch category 4
References:	Oelkers, H.A. 1965. Theor. Med. 19:625. In BIBRA. 1993. Toxicology Profile: Citric acid and its common salts. BIBRA International.

(k)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Rat (Wistar)
Value:	8,610 mg/kg b.w.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* A group of 30 albino male and female rats (five per dose) were given either 1.0, 2.0, 4.0, 8.0, 16.0 or 32.0 g/kg bw of acetic acid, magnesium salt in propylene glycol via intubation.
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Acetic Acid, Magnesium Salt (142-72-3)
Remarks:	No toxic effects were noted at the 1.0 and 2.0 g/kg doses. Diarrhea and ruffled unkempt coats were evident 24-36 hours after intubation at the 4.0 g/kg dose. Deaths in the 16.0 and 32.0 g/kg doses occurred 8-16 hours and within 6 hours, respectively.
Reliability:	Klimisch category 2
References:	Green, L.A. 1977. Toxicity Studies for The Shepherd Chemical Company: Acute Oral LD_{50} Toxicity Study: Magnesium Acetate. Bio-Toxicology Laboratories, May 31, 1977.

(l)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Rat
Value:	3,730 mg/kg b.w.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Rats were given a single oral dose of 200,000 mg/L (0.200 g/ml) of acetic acid, manganese salt in water via intubation. A range-finding toxicity test was conducted as described in Smyth et al. 1962.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Manganese Salt (638-38-0)
Reliability:	Klimisch category 2
References:	Smyth, H.F., Jr., Carpenter, C.P., Weil, C.S., Pozzani, U.C., Striegel, J.A., and Nycum, J.S. 1969. Range-finding toxicity data: List VII. Am. Ind. Hyg. Assoc. J. 30:470-476. Smyth, H.F. Jr., Carpenter, C.P., Weil, C.S., Pozzani, U.C., and Striegel, J.A. 1962. Range-finding toxicity data: List VI. Amer. Ind. Hyg. Assoc. J. 23:95-207.

5.1.2 ACUTE INHALATION TOXICITY

(a)

Type:	LC_0 [ ]; LC_{100} [ ]; LC_{50} [X]; LCL_0 [ ]; Other [ ]
Species/strain:	Rat
Exposure period:	4 hours
Value:	11.4 mg/l
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* BASF-Test Protocol
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Acetic Acid (64-19-7); purity: 96%
Reliability:	Klimisch category 2
References:	BASF, A.G. 1989. Unpublished study No. 78/650, 21.05.1980. In European Commission. 1996. Acetic acid. International Uniform Chemical Information Database.

(b)

Type:	LC_0 [ ]; LC_{100} [ ]; LC_{50} [X]; LCL_0 [ ]; Other [ ]
Species/strain:	Mouse
Exposure period:	1 hour
Value:	5,620 ppm
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid (64-19-7)
Remarks:	Inhalation of > 1,000 ppm produced irritation of the conjunctiva and upper respiratory tract.
Reliability:	Klimisch category 4
References:	Ghiringhelli, L. and Difabio, A. 1957. Med. Lav. 48: 559. In Clayton, G.D. and Clayton, F.E. (eds.). 1994. Patty's Industrial Hygiene and Toxicology. Volume II, Part E. Toxicology. New York: John Wiley & Sons, Inc.

(c)

Type:	LC_0 [ ]; LC_{100} [ ]; LC_{50} [X]; LCL_0 [ ]; Other [ ]
Species/strain:	Rat
Exposure period:	1 hour
Value:	>30 g/m^3
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Sodium Salt (127-09-3)
Reliability:	Klimisch category 4

References: BIOFAX Industrial Bio-Test Laboratories, Inc. 1971. Data sheets. 19-3. In Registry of Toxic Effects of Chemical Substances. 1999. Sodium acetate. National Institute for Occupational Safety and Health.

5.1.3 ACUTE DERMAL TOXICITY

(a)

Type: LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain: Rabbit
Value: 1060 mg/kg b.w
Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]
Test substance: Acetic Acid (64-19-7)
Reliability: Klimisch category 4
References: Union Carbide Corporation. 1963. Union Carbide data sheet. Union Carbide Corporation. Industrial Medicine & Technology. In European Commission. 1996. Acetic acid. International Uniform Chemical Information Database.

(b)

Type: LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain: Rabbit
Value: > 20,000 mg/kg b.w.
Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
Dose was administered via a single skin penetration to three female albino New Zealand rabbits and kept in place by gauze patches under a latex rubber film.
GLP: Yes [ ] No [ ] ? [X]
Test substance: Fumaric Acid (110-17-8)
Remarks: No mortality was observed at the high dose of 20,000 mg/kg b.w.
Reliability: Klimisch category 2
References: Vernot, E.H., MacEwen, J.D., Haun, C.C., and Kinkead, E.R. 1977. Acute toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. Toxicol. Appl. Pharmacol. 42:417-423.

(c)

Type: LD_0 [ ]; LD_{100} [ ]; LD_{50} [ ]; LDL_0 [ ]; Other [X]
Species/strain: Rabbit
Results: 3 minute exposure = very slight erythema (hair on site); no edema
24 and 48 hrs after 3 minute exposure = no erythema and no edema
60 minute exposure = very slight erythema; no edema

	24 and 48 hrs after 60 minute exposure = no erythema; no edema 4hr exposure = very slight-moderate to severe erythema; very slight – moderate edema 24 hrs after 4 hr exposure = very slight-moderate to severe erythema; very slight – moderate edema 48 hrs after 4 hr exposure = Well defined erythema; slight – no edema
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* According to DOT 3-1/10-07-91/REV5 (49 CFR). Young adult, New Zealand White rabbits (five males and three females) were used in this study. The test material was initially applied to one animal for a 3 minute exposure period. Due to the absence of skin corrosion in this initial animal, a second animal was initiated utilizing a 60 minute exposure period. Due to the absence of skin corrosion for the 60 minute exposure period, the test material was ultimately administered to six additional animals for an exposure period of 4 hours. Each animal received on 0.5 ml quantity of undiluted test material each of which was applied in this manner to one intact skin site per animal. Three (3) minute, twenty-four (24), and forty-eight (48) hour skin scores, derived from the intact skin site were evaluated for corrosion in the rabbit receiving a three minute exposure period. Sixty (60) minute, twenty-four (24), and forty-eight(48) hour skin scores, derived from the intact skin site were evaluated for corrosion in the rabbit receiving a sixty minute exposure period. Four (4), twenty-four (24), and forty-eight (48) hour skin scores, derived from the intact skin site were evaluated for corrosion in the rabbit receiving a four hour exposure period.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid (77-92-9), purity: 60%
Remarks:	Corrosion was considered to have occurred if the substance in contact with the intact rabbit skin caused destruction or irreversible alteration of the tissue of two or more rabbits. Tissue destruction was considered to have occurred if, at any of the readings, there was ulceration or necrosis. Test generally follows GLP procedures.
Reliability:	Klimisch category 2

References: Hill Top Biolabs, Inc. 1992. D.O.T. corrosivity potential study in rabbits of : Citric acid solution, 60% for Cargill, Inc. Hill Top Biolabs project No. 92-8758-21 (A). Cargill, Inc. Project No. ED76904.

5.1.4 ACUTE TOXICITY BY OTHER ROUTES OF ADMINISTRATION

(e.g. subcutaneous, intravenous, etc.)

(a)

Type: LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]

Species/strain: Mouse

Route of Administration: i.m. [ ]; i.p. [ ]; i.v. [X]; Infusion [ ]; s.c. [ ]; Other [ ]

Value: 525 mg/kg b.w.

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
Not stated

GLP: Yes [ ] No [ ] ? [X]

Test substance: Acetic Acid (64-19-7)

References: Oro, L. and Wretlind, A. 1961. Acta Pharmacol. 18:141. In Clayton, G.D. and Clayton, F.E. (eds.). 1994. Patty's Industrial Hygiene and Toxicology. Volume II, Part E. Toxicology. New York: John Wiley & Sons, Inc.

(b)

Type: LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]

Species/strain: Rat

Route of Administration: i.m. [ ]; i.p. [X]; i.v. [ ]; Infusion [ ]; s.c. [ ]; Other [ ]

Value: 632 mg/kg b.w.

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
Not stated

GLP: Yes [ ] No [ ] ? [X]

Test substance: Acetic Acid, Ammonium Salt (631-61-8)

References: Lewis, R.T. (ed.) 1994. Sax's Dangerous Properties of Industrial Materials. Eighth Edition. New York: Van Nostrand Reinhold Company.

(c)

Type: LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]

Species/strain: Mouse

Route of Administration: i.m. [ ]; i.p. [ ]; i.v. [X]; Infusion [ ]; s.c. [ ]; Other [ ]

Value: 98 mg/kg b.w.

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
Not stated

GLP: Yes [ ] No [ ] ? [X]
Test substance: Acetic Acid, Ammonium Salt (631-61-8)
References: Lewis, R.T. (ed.) 1994. Sax's Dangerous Properties of Industrial Materials. Eighth Edition. New York: Van Nostrand Reinhold Company.

(d)
Type: LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain: Mouse
Route of Administration: i.m. [ ]; i.p. [ ]; i.v. [X]; Infusion [ ]; s.c. [ ]; Other [ ]
Value: 52 mg/kg b.w.
Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]
Test substance: Acetic Acid, Calcium Salt (62-54-4)
References: Welch et al. 1944. J. Lab. Clin. Med. 29:809. In Lewis, R.T. (ed.). 1994. Sax's Dangerous Properties of Industrial Materials. Eighth Edition. New York: Van Nostrand Reinhold Company.

(e)
Type: LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain: Mouse
Route of Administration: i.m. [ ]; i.p. [ ]; i.v. [ ]; Infusion [ ]; s.c. [X]; Other [ ]
Value: 3,200 mg/kg b.w.
Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
Mice were C3H strain and weighed 25 ± 5g.
GLP: Yes [ ] No [X] ? [ ]
Test substance: Acetic Acid, Sodium Salt (127-09-3)
Reliability: Klimisch category 2
References: Allen, H.R., Tucker, R.K., and Geren, C.R. 1986. Potentiation of the toxicity of basic peptides from rattlesnake venoms by acetic acid, sodium salt. Toxicon 24(6):553-558.

(f)
Type: LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; LD_0 [ ]; LD_{100} [ ]; LD_{50} [ ]; LDL_0 [ ]; Other [X]
Species/strain: Rat
Route of Administration: i.m. [ ]; i.p. [X]; i.v. [ ]; Infusion [ ]; s.c. [ ]; Other []
Results: 10 mg/kg injected intraperitoneally in rats causes hepatotoxicity, tremors, and hypothermia. 100 mg/kg decreases motor activity and causes diuresis.
Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]

Test substance:	Fumaric Acid (110-17-8)
References:	Mileski, D.R., Kaplan, H.R., Malone, M.H., and Nieforth, K.A. 1965. J. Pharm. Sci. 54: 295. In Clayton, G.D. and Clayton, F.E. (eds.). 1994. Patty's Industrial Hygiene and Toxicology. 4th Ed. Volume II, Part E: Toxicology. John Wiley & Sons, Inc.
(g)	
Type:	LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Mouse
Route of Administration:	i.m. [ ]; i.p. [X]; i.v. [ ]; Infusion [ ]; s.c. [ ]; Other [ ]
Value:	200 mg/kg b.w.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Analyzed using Behren's method which is described in Statistical Methods in Biological Assay. 1952. p.535.
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Fumaric Acid (110-17-8)
Remarks:	Data as cited in Smith. Data from Upjohn Dept of Pharmacology.
Reliability:	Klimisch category 2
References:	Smith, C.G., Grady, J.E., and Northam, J.I. 1963. Relationship between cytotoxicity in vitro and whole animal toxicity. Cancer Chemother. Rep. 30:9-12.
(h)	
Type:	LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Rat
Route of Administration:	i.m. [ ]; i.p. [X]; i.v. [ ]; Infusion [ ]; s.c. [ ]; Other [ ]
Value:	100 mg/kg
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Malic Acid (6915-15-7)
References:	Eastman Kodak. 1981. Health Safety and Human Factors Laboratory, Rochester, New York. In BIBRA. 1992. Toxicology profile: Malic acid and its common salts. BIBRA International.
(i)	
Type:	LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Rat
Route of Administration:	i.m. [ ]; i.p. [ ]; i.v. [ ]; Infusion [ ]; s.c. [X]; Other [ ]
Value:	5500 mg/kg

Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Six 5-week old male SD-JCL rats weighing 110-140 g were used at each dosage group. A single oral dose was administered for each of a series of concentrations in volumes of 2 ml/100 g body weight. Behavior and mortality were observed for 7 days.
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Citric Acid (77-92-9); purity: 99.8% citric acid monohydrate
Remarks:	Observed effects include respiratory failure and emaciation.
Reliability:	Klimisch category 2
References:	Yokotani, H., Usui, T., Nakaguchi, T., Kanabayashi, T. Tanda, M., and Aramaki, Y. 1971. Acute and subacute toxicological studies of TAKEDA-citric acid in mice and rats. J. Takeda Res. lab. 30(1):25-31.

(j)

Type:	LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Mouse
Route of Administration:	i.m. [ ]; i.p. [ ]; i.v. [ ]; Infusion [ ]; s.c. [X]; Other [ ]
Value:	2700 mg/kg
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Six 4-week old male ICR-JCL mice weighing 20-24 g were used at each dosage group. A single oral dose was administered for each of a series of concentrations in volumes of 2 ml/100 g body weight. Behavior and mortality were observed for 7 days.
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Citric Acid (77-92-9); purity: 99.8% citric acid monohydrate
Remarks:	Observed effects include respiratory failure and emaciation.
Reliability:	Klimisch category 2
References:	Yokotani, H., Usui, T., Nakaguchi, T., Kanabayashi, T. Tanda, M., and Aramaki, Y. 1971. Acute and subacute toxicological studies of TAKEDA-citric acid in mice and rats. J. Takeda Res. lab. 30(1):25-31.

(k)

Type:	LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; LD_0 [ ]; LD_{100} [ ]; LD_{50} [ ]; LDL_0 [ ]; Other [X]
Species/strain:	Horse
Route of Administration:	i.m. [ ]; i.p. [ ]; i.v. [X]; Infusion [ ]; s.c. [ ]; Other [ ]
Results:	No significant cardiovascular effects or effects on blood composition in horses injected with 0.56 mg/kg b.w. of citric acid, sodium salt.

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
Six horses were used.
GLP: Yes [ ] No [ ] ? [X]
Test substance: Citric Acid, Sodium Salt (994-36-5)
References: Hubbell, J.A.E., et al. 1987. Vet. Surg. 16:245. In BIBRA. 1993. Toxicology profile: Citric acid and its common salts. BIBRA International.

(l)
Type: LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain: Rat
Route of Administration: i.m. [ ]; i.p. [X]; i.v. [ ]; Infusion [ ]; s.c. [ ]; Other [ ]
Value: 1,348 mg/kg b.w.
Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]
Test substance: Monosodium citrate (18996-35-5)
References: Journal of Pharmacol. Exp. Therapeutics. 1948. 94:65. In Lewis, R.T. (ed.). 1994. Sax's Dangerous Properties of Industrial Materials. Eighth Edition. New York: Van Nostrand Reinhold Company.

(m)
Type: LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain: Mouse
Route of Administration: i.m. [ ]; i.p. [X]; i.v. [ ]; Infusion [ ]; s.c. [ ]; Other [ ]
Value: 1,635 mg/kg b.w.
Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]
Test substance: Monosodium citrate (18996-35-5)
References: J. of Pharmacol. Exp. Therapeutics. 1948. 94:65. In Lewis, R.T. (ed.). 1994. Sax's Dangerous Properties of Industrial Materials. Eighth Edition. New York: Van Nostrand Reinhold Company.

(n)
Type: LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain: Dog
Route of Administration: i.m. [ ]; i.p. [ ]; i.v. [X]; Infusion [ ]; s.c. [ ]; Other [ ]
Value: 167 mg/kg b.w.
Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]

Test substance:	Citric Acid, Tripotassium Salt (866-84-2)
References:	American Veterinary Review. 1937. 44:555. In Lewis, R.T. (ed.). 1994. Sax's Dangerous Properties of Industrial Materials. Eighth Edition. New York: Van Nostrand Reinhold Company.

(o)

Type:	LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Rat
Route of Administration:	i.m. [ ]; i.p. [X]; i.v. [ ]; Infusion [ ]; s.c. [ ]; Other [ ]
Value:	1,548 mg/kg b.w.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid, Trisodium Salt (64-08-2)
Remarks:	Effects noted at the high concentrations included convulsions or effect on seizure threshold; cyanosis; changes in structure or function of salivary glands.
Reliability:	Klimisch category 4
References:	J. of Pharmacol. Exp. Therapeutics. 1948. 94:65. In Registry of Toxic Effects of Chemical Substances. 1999. Trisodium citrate. National Institute for Occupational Safety and Health.

(p)

Type:	LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Mouse
Route of Administration:	i.m. [ ]; i.p. [X]; i.v. [ ]; Infusion [ ]; s.c. [ ]; Other [ ]
Value:	1,364 mg/kg b.w.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid, Trisodium Salt (64-08-2)
Remarks:	Effects noted at the high concentrations included convulsions or effect on seizure threshold; cyanosis; changes in structure or function of salivary glands.
Reliability:	Klimisch category 4
References:	J. of Pharmacol. Exp. Therapeutics. 1948. 94:65. In Registry of Toxic Effects of Chemical Substances. 1999. Trisodium citrate. National Institute for Occupational Safety and Health.

(q)

Type:	LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Mouse
Route of Administration:	i.m. [ ]; i.p. [ ]; i.v. [X]; Infusion [ ]; s.c. [ ]; Other [ ]

Value:	170 mg/kg b.w.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid, Trisodium Salt (64-08-2)
Remarks:	Effects noted at the high concentrations included convulsions or effect on seizure threshold; cyanosis; changes in structure or function of salivary glands.
Reliability:	Klimisch category 4
References:	J. of Pharmacol. Exp. Therapeutics. 1948. 94:65. In Registry of Toxic Effects of Chemical Substances. 1999. Trisodium citrate. National Institute for Occupational Safety and Health.

(r)

Type:	LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Rabbit
Route of Administration:	i.m. [ ]; i.p. [ ]; i.v. [X]; Infusion [ ]; s.c. [ ]; Other [ ]
Value:	449 mg/kg b.w.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid, Trisodium Salt (64-08-2)
Remarks:	Effects noted at the high concentrations included convulsions or effect on seizure threshold; cyanosis; changes in structure or function of salivary glands.
Reliability:	Klimisch category 4
References:	J. of Pharmacol. Exp. Therapeutics. 1948. 94:65. In Registry of Toxic Effects of Chemical Substances. 1999. Trisodium citrate. National Institute for Occupational Safety and Health.

(s)

Type:	LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Mouse
Route of Administration:	i.m. [ ]; i.p. [ ]; i.v. [X]; Infusion [ ]; s.c. [ ]; Other [ ]
Value:	111 mg/kg b.w.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Magnesium Salt (142-72-3)
Reliability:	Klimisch category 4
References:	J. Clin. Lab. Med. 1944. 29: 804. In Registry of Toxic Effects of Chemical Substances. 2000. Acetic acid, magnesium salt. National Institute for Occupational Safety and Health.

5.4 REPEATED DOSE TOXICITY

(a)

Species/strain:	Rat
Sex:	Female [ ]; Male [X]; Male/Female [ ]; No Data [ ]
Route of Administration:	oral
Exposure period:	8 months
Frequency of treatment:	3 times per week
Dose:	0.5 ml of 3% water solution of acetic acid (about 60 mg/kg bw/treatment)
Control group:	Yes [ ]; No [X]; No Data [ ] Concurrent no treatment [ ]; Concurrent vehicle [ ]; Historical [ ]
Results:	As expected, rats treated with the carcinogen NSEE had high incidences of pre-neoplastic lesions of the esophagus and forestomach, as well as benign tumors, carcinomas and squamous cell cancer. Prolonged administration of acetic acid in combination with NSEE resulted in an increase in the number of benign and malignant tumors and carcinomas in the esophagus. Prolonged administration of acetic acid alone did not induce tumors. All nine of these rats, however, did experience hyperplasia in the esophagus and forestomach.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Nine outbred white male rats weighing approximately 100 g were used in the acetic acid alone study. Rats were given either N-nitrosarcosin ethyl ester (NSEE; a known carcinogen) alone, NSEE with the acetic acid solution, or the acetic acid solution alone. All doses were given by intubation into the esophagus. Animals were killed by ether inhalation after 8 months of experiments and autopsied.
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Acetic acid (64-17-9)
Reliability:	Klimisch category 2
References:	Alexandrov, V.A., Novikov, A.I., Zabezhinsky, M.A., Stolyarov, V.I., and Petrov, A.S. 1989. The stimulating effect of acetic acid, alcohol, and thermal burn injury on esophagus and forestomach carcinogenesis induced by n-nitrososarcosin ethyl ester in rats. Cancer Lett. 47:79-185.

(b)

Species/strain:	Rat and mouse
Sex:	Female [ ]; Male [ ]; Male/Female [ ]; No Data [X]
Route of Administration:	Inhalation
Exposure period:	3-35 days
Frequency of treatment:	Continuous

Dose:	11-35 ppm
Control group:	Yes [ ]; No [ ]; No Data [X] Concurrent no treatment [ ]; Concurrent vehicle [ ]; Historical [ ]
Results:	At 15 ppm (for 22 days) or more, the animals showed decreased activity, behavioral changes and reduced work capacity. At 23-31 ppm (17-35 days), there was decreased growth, increased spleen weight, an increase of the level of iron stored in the spleen, signs of kidney damage and increased kidney weights.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Groups of at least 10 rats and 10 mice were used.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid (64-19-7)
Reliability:	Klimisch category 2
References:	Savina, V.P. and Anisimov, B.V. 1987. Kosm. Biol. Aviakosm. Med. 21:79. In BIBRA. 1993. Toxicology profile: Acetic acid and its common salts. BIBRA International.

(c)

Species/strain:	Rat (Long-Evans hooded)
Sex:	Female [ ]; Male [X]; Male/Female [ ]; No Data [ ]
Route of Administration:	oral (in drinking water)
Exposure period:	8 months
Frequency of treatment:	daily *ad libitum*
Dose:	50 and 500 ppm
Control group:	Yes [ ]; No [X]; No Data [ ] Concurrent no treatment [ ]; Concurrent vehicle [ ]; Historical [ ]
NOAEL:	500 ppm
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Long-Evans hooded rats 21 days old at test initiation were used. The test material was administered *ad libitum* for eight months.
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Acetic Acid, Sodium Salt (127-09-3)
Remarks:	No significant effects on survival, reinforcement behavior, or body weight gain were observed. The rats treated with acetic acid, sodium salt served as the control for a lead exposure study. Therefore, no separate untreated controls are available for comparison.
Reliability:	Klimisch category 2
References:	Cory-Slechta, D.A. 1986. Neurobehav. Toxicol. Teratol. 8:237-244. In European Commission. 1996. Sodium acetate. International Uniform Chemical Information Database.

(d)

Species/strain:	Rat
Sex:	Female [ ]; Male [ ]; Male/Female [ ]; No Data [X]
Route of Administration:	oral in diet
Exposure period:	4 weeks
Frequency of treatment:	daily
Dose:	3.58% of the diet (approx. 3.6 g/kg b.w./day)
Control group:	Yes [ ]; No [ ]; No Data [X] Concurrent no treatment [ ]; Concurrent vehicle [ ]; Historical [ ]
Results:	Growth and survival were normal.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* 13 young rats were used.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Sodium Salt (127-09-3)
Reliability:	Klimisch category 2
References:	Dryden, L.P. and Hartman, A.M. 1971. J. Nutr. 101:589. In BIBRA. 1993. Toxicology profile: Acetic acid and its common salts. BIBRA International.

(e)

Species/strain:	Rat
Sex:	Female [ ]; Male [X]; Male/Female [ ]; No Data [ ]
Route of Administration:	oral in drinking water
Exposure Period:	112 days, beginning at 31 days of age
Frequency of treatment:	Continuous
Dose:	100 ppm
Control group:	Yes [X]; No [ ]; No Data [ ] Concurrent no treatment [X]; Concurrent vehicle [ ]; Historical [ ]
Results:	No mortality or cognitive impairment was observed.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Eight young adult male Wistar rats were exposed to acetic acid, sodium salt in their drinking water. Training in mazes began on day 112 and lasted until day 157 at which time all animals were sacrificed.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Sodium Salt (127-09-3)
Remarks:	The rats treated with acetic acid, sodium salt served as the control for a lead exposure study. Therefore, no untreated controls are available for comparison.
Reliability:	Klimisch category 2
References:	Massaro, E.J. and Massaro, T.F. 1987. Low level lead exposure during neonatal development perturbs cognitive function. J. Am. Coll. Toxicol. 6(4):441-450.

(f)

Species/strain:	Rat
Sex:	Female [ ]; Male [ ]; Male/Female [ ]; No Data [X]
Route of Administration:	oral in diet
Exposure period:	3 months
Frequency of treatment:	daily
Dose:	21 mg/kg b.w./day
Control group:	Yes [ ]; No [ ]; No Data [X] Concurrent no treatment [ ]; Concurrent vehicle [ ]; Historical [ ]
Results:	Indications of altered thyroid function and decreased growth were reported.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Ten rats were used.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Sodium Salt (127-09-3)
Reliability:	Klimisch category 2
References:	Goldman, M. 1981. Experientia 37:1348. In BIBRA. 1993. Toxicology profile: Acetic acid and its common salts. BIBRA International.

(g)

Species/strain:	Rat
Sex:	Female [ ]; Male [ ]; Male/Female [X]; No Data [ ]
Route of Administration:	oral in diet
Exposure period:	2 years
Frequency of treatment:	daily
Dose:	female and male rats: 0.1, 0.5, 0.8 or 1.2% fumaric acid male rats: 0.5, 1, or 1.5% fumaric acid
Control group:	Yes [ ]; No [ ]; No Data [X] Concurrent no treatment [ ]; Concurrent vehicle [ ]; Historical [ ]
Results:	Slightly increased mortality and increased incidence of testes degeneration were observed in rats fed 1.5% fumaric acid (approximately 750 mg/kg b.w/day). Two rats receiving 1% or 0.5% had stomach inflammation.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Groups of 12 male and 12 female rats or groups of just male rats were fed the stated doses in the diet.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Fumaric Acid (110-17-8)
Reliability:	Klimisch category 2
References:	Fitzhugh, O.G. and Nelson, A.A. 1947. J. Am. Pharm. Assoc. 36:217. In BIBRA. 1991. Toxicology profile: Fumaric acid and its common salts. BIBRA International.

(h)

Species/strain:	Rat
Sex:	Female [ ]; Male [ ]; Male/Female [ ]; No Data [X]
Route of Administration:	Oral
Exposure period:	2 years
Frequency of treatment:	Daily
Dose:	0.05, 0.5 or 5% in diet (equivalent to 2-200 mg/kg bw/day)
Control group:	Yes [X]; No [ ]; No Data [ ] Concurrent no treatment [ ]; Concurrent vehicle [ ]; Historical [ ]
Results:	No tissue abnormalities or changes in the blood or urine were observed. Changes in organ weights, and in the first year, decreased growth, and hunched appearance were observed in rats receiving 200 mg/kg bw/day.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Malic Acid (6915-15-7)
Remarks:	The percent in diet is stated to be equivalent to 2-200 mg kg b.w./day, but BIBRA notes that the values in the region of 25-2,500 mg/kg b.w./day seem more likely.
Reliability:	Klimisch category 2
References:	Hazleton Laboratories. 1971. 24-Month dietary administration-rats and 104-week dietary administration-dogs [Material X-5120]. Final reports submitted to Allied Chemical Corporation, Buffalo, New York. In BIBRA. 1992. Toxicology profile: Malic acid and its common salts. BIBRA International.

(i)

Species/strain:	Rabbit
Sex:	Female [ ]; Male [ ]; Male/Female [ ]; No Data [X]
Route of Administration:	oral in diet
Exposure period:	150 days
Frequency of treatment:	daily
Dose:	7.7% citric acid, sodium salt (~5% free acid)
Control group:	Yes [X]; No [ ]; No Data [ ] Concurrent no treatment [X]; Concurrent vehicle [ ]; Historical [ ]
Results:	No gross or histopathological changes or difference in growth or survival found.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Rabbits were exposed to citric acid, sodium salt in the diet for 150 days.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid (77-92-9)
Reliability:	Klimisch category 2

References:	Packman, E.W., Abbott, D.D., and Harrison, J.W.E. 1963. Toxicol. Appl. Pharmacol. 5:163. In Clayton, G.D. and Clayton, F.E. (eds.). 1994. Patty's Industrial Hygiene and Toxicology. 4th Ed. Volume II, Part E: Toxicology. John Wiley & Sons, Inc.

(j)

Species/strain:	Rat (Sprague-Dawley)
Sex:	Female [ ]; Male [X]; Male/Female [ ]; No Data [ ]
Route of Administration:	oral in diet
Exposure period:	6 weeks
Frequency of treatment:	daily
Post exposure observation period:	none
Dose:	0.2, 2.4, and 4.8%
Control group:	Yes [X]; No [ ]; No Data [ ] Concurrent no treatment [X]; Concurrent vehicle [ ]; Historical [ ]
NOEL:	2,260 mg/kg bw
LOAEL:	4,670 mg/kg bw
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Male SD-JCL rats weighing 98 to 112 g, and 29 to 35 days old at test initiation were fed citric acid in the diet. Four groups of 10 animals each were maintained at 23 ± 1°C for 6 weeks. Body weight was measured in all animals 2 times per week, food intake was measured in a group of five animals twice per week, and any behavioral abnormalities were observed daily.
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Citric Acid (77-92-9); purity: 99.8% citric acid monohydrate
Remarks:	No behavioral abnormalities, effects on body weight gain, or mortality were observed. Some minor biochemical changes were observed with the highest dose, but no specific pathohistological abnormalities were detected.
Reliability:	Klimisch category 2
References:	Yokotani, H., Usui, T., Nakaguchi, T., Kanabayashi, T. Tanda, M., and Aramaki, Y. 1971. Acute and subacute toxicological studies of TAKEDA-citric acid in mice and rats. J. Takeda Res. lab. 30(1):25-31.

(k)

Species/strain:	Rat
Sex:	Female [ ]; Male [ ]; Male/Female [ ]; No Data [X]
Route of Administration:	oral in diet
Exposure period:	~ 1 year
Frequency of treatment:	daily
Dose:	0.1%

Control group:	Yes [X]; No [ ]; No Data [ ] Concurrent no treatment [X]; Concurrent vehicle [ ]; Historical [ ]
Results:	No adverse effects were found.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Two successive generations of rats were fed 0.1% citric acid, sodium salt in the diet.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid, Sodium Salt (994-36-5)
Remarks:	A limited number of tissues were examined microscopically.
Reliability:	Klimisch category 2
References:	Bonting, S.L., and Jansen, B.C.P. 1956. Voeding 17: 137. In BIBRA. 1993. Toxicology profile: Citric acid and its common salts. BIBRA International.

(l)

Species/strain:	Rat
Sex:	Female [ ]; Male [X]; Male/Female [ ]; No Data [ ]
Route of Administration:	oral in diet
Exposure period:	32 weeks
Frequency of treatment:	daily
Dose:	5% (~2,500 mg/kg b.w./day)
Control group:	Yes [X]; No [ ]; No Data [ ] Concurrent no treatment [X]; Concurrent vehicle [ ]; Historical [ ]
Results:	No overt signs of toxicity were observed.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Twenty male rats were fed 5% citric acid, sodium salt in the diet for 32 weeks (about 2,500 mg/kg b.w./day).
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid, Sodium Salt (994-36-5)
Reliability:	Klimisch category 2
References:	Fukushima, S., et al. 1986. Gann 77:1. In BIBRA. 1993. Toxicology profile: Citric acid and its common salts. BIBRA International

(m)

Species/strain:	Mouse
Sex:	Female [ ]; Male [X]; Male/Female [ ]; No Data [ ]
Route of Administration:	oral feed
Exposure period:	12 months
Frequency of treatment:	Continuous in the diet
Post exposure observation period:	None
Dose:	2 g Mn/kg of food in the form of acetic acid, manganese salt
Control group:	Yes [X]; No [ ]; No Data [ ] Concurrent no treatment [X]; Concurrent vehicle [ ]; Historical [ ]

Results:	No mortality was observed during the experiment. By the end of the study, body weight gain was significantly suppressed in the treatment mice compared to the controls (P<0.05). When body weight gain became less than that of the control, changes in spontaneous motor activity were noted. In the hypothalamus, dopamine levels decreased significantly (P< 0.05) and the manganese content increased up to 13 times compared to the controls.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Six-week old male ddY mice weighing 29.1± 0.2 g were divided into two groups with six mice in each. The first group served as the control and the second received 2 g Mn/kg in the form of acetic acid, manganese salt in the diet for twelve months. All animals were allowed free access to food and water. Body weight changes were recorded and spontaneous motor activity was tested. Urine, blood, and tissue samples were analyzed. Mice were decapitated 24 hours after last feeding.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Manganese Salt (638-38-0)
Reliability:	Klimisch category 2
References:	Komura, J. and Sakamoto, M. 1992. Effects of manganese forms on biogenic amines in the brain and behavioral alterations in the mouse: Long-term oral administration of several manganese compounds. Environ. Res. 57(1):34-44.

5.5 GENETIC TOXICITY *IN VITRO*

A. Bacterial Test

(a)

Type:	Bacterial reverse mutation assay
System of testing:	TA 98, TA 100, TA 1535, TA 1537, and TA 1538
Metabolic activation:	With [ ]; Without [ ]; With and Without [X]; No Data [ ]

Results:

Genotoxic effects:	+	?	-
With metabolic activation:	[ ]	[ ]	[X]
Without metabolic activation:	[ ]	[ ]	[X]

Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Ames test
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid (64-19-7)
Reliability:	Klimisch category 2

References: NcMahon et al. 1979. Cancer Res. 39:682-693. In European Commission. 1996. Acetic acid. International Uniform Chemical Information Database.

(b)

Type: Bacterial reverse mutation assay

System of testing: *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 97 and/or TA 1537.

Concentration: 100, 333, 1000, 3333, 6666, 10000 µg/plate

Metabolic activation: With [ ]; Without [ ]; With and Without [X]; No Data [ ]

Results:

Genotoxic effects:	+	?	-
With metabolic activation:	[ ]	[ ]	[X]
Without metabolic activation:	[ ]	[ ]	[X]

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]* Standard Ames test.

GLP: Yes [X] No [ ] ? [ ]

Test substance: Acetic Acid (64-19-7), purity: 99%

Remarks: Tested within the National Toxicology Program's mutagenicity testing program.

Reliability: Klimisch category 1

References: Zeiger, E., Anderson, B., Haworth, S. Lawlor, T., and Mortelmans, K. 1992. Salmonella mutagenicity test: V. results from the testing of 311 chemicals. Environ. Mol. Mutagen. 19(Suppl. 21):2-141.

(c)

Type: Bacterial reverse mutation assay

Metabolic activation: With [ ]; Without [ ]; With and Without [X]; No Data [ ]

Results: Acetic acid and its sodium and zinc salts have given no evidence of mutagenic activity in good-quality Ames tests using *Salmonella typhimurium* either with or without S9.

Genotoxic effects:	+	?	-
With metabolic activation:	[ ]	[ ]	[X]
Without metabolic activation:	[ ]	[ ]	[X]

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]* Ames test

GLP: Yes [ ] No [ ] ? [X]

Test substance: Acetic Acid (64-19-7); Acetic Acid, Sodium Salt (127-09-3)

Reliability: Klimisch category 2

References: BIBRA. 1993. Toxicology profile: Acetic acid and its common salts. BIBRA International.

(d)

Type:	Bacterial reverse mutation assay
System of testing:	*Salmonella typhimurium* strains TA 92, TA 94, TA 98, TA 100, TA 1535, and TA 1537,
Concentration:	maximum concentration of 40 mg/plate
Metabolic activation:	With [X]; Without [ ]; With and Without [ ]; No Data [ ]
Results:	
Genotoxic effects:	+ ? -
	With metabolic activation: [ ] [ ] [X]
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* An Ames test was conducted using the test substance in a phosphate buffer. Six concentrations were tested. Two plates were used for each concentration.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Sodium Salt (127-09-3)
Reliability:	Klimisch category 2
References:	Ishidate, M., Jr., Sofuni, T., Yoshikawa, K., Hayashi, M., Nohmi, T., Sawada, M., and Matsouka, A. 1984. Primary mutagenicity screening of food additives currently used in Japan. Fd. Chem. Toxic. 22(8):623-636.

(e)

Type:	Bacterial reverse mutation assay
System of testing:	*Salmonella typhimurium* strains TA 98, TA100, TA 1535, TA 97 and/or TA1537
Concentration:	Not stated
Metabolic activation:	With [ ]; Without [ ]; With and Without [X]; No Data [ ]
Results:	
Genotoxic effects:	+ ? -
	With metabolic activation: [ ] [ ] [X]
	Without metabolic activation: [ ] [ ] [X]
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Ames test.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Fumaric Acid (110-17-8)
Reliability:	Klimisch category 2
References:	Zeiger, E., et al. 1988. Environ. Molec. Mutagen. 11:1. In BIBRA. 1991. Toxicology profile: Fumaric acid and its common salts. BIBRA International.

(f)

Type:	Bacterial reverse mutation assay
System of testing:	*Salmonella typhimurium* strain TA 100
Concentration:	1000, 100, 10, 1, and 0.1 µg/plate
Metabolic activation:	With [ ]; Without [X]; With and Without [ ]; No Data [ ]

Results:

Genotoxic effects:

	+	?	-
Without metabolic activation:	[ ]	[ ]	[X]

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
An Ames test was conducted using a constant volume of 0.4 ml of fumaric acid at concentrations of 1000, 100, 10, 1, and 0.1 µg/plate.

GLP: Yes [ ] No [ ] ? [X]
Test substance: Fumaric Acid (110-17-8)
Reliability: Klimisch category 2
References: Rapson, W.H., Nazar, M.A., and Butsky, V.V. 1980. Mutagenicity produced by aqueous chlorination of organic compounds. Bull. Environm. Toxicol. 24:590-596.

(g)
Type: Bacterial reverse mutation assay
System of testing: *Salmonella typhimurium* strains TA 97, TA 98, TA 100, and TA 104
Concentration: 0, 1100, 1500, and 2000 µg/plate
Metabolic activation: With [ ]; Without [ ]; With and Without [X]; No Data [ ]

Results:

Genotoxic effects:

	+	?	-
With metabolic activation:	[ ]	[ ]	[X]
Without metabolic activation:	[ ]	[ ]	[X]

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
Ames Salmonella/microsome test. All tests were done in triplicate both with and without S9 activation.

GLP: Yes [ ] No [ ] ? [X]
Test substance: Malic Acid (6915-15-7)
Reliability: Klimisch category 2
References: Al-Ani, F.Y. and Al-Lami, S.K. 1988. Absence of mutagenic activity of acidity regulators in the ames salmonella/microsome test. Mutat. Res. 206:467-470.

(h)
Type: Bacterial reverse mutation assay
System of testing: *Salmonella typhimurium* strains TA 97, TA 98, TA 100, and TA 104
Concentration: 0, 500, 1000, and 2000 µg/plate
Metabolic activation: With [ ]; Without [ ]; With and Without [X]
Results:

Genotoxic effects:

	+	?	-
With metabolic activation:	[ ]	[ ]	[X]
Without metabolic activation:	[ ]	[ ]	[X]

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
Ames *Salmonella*/microsome test. All tests were done in triplicate both with and without S9.

GLP: Yes [ ] No [ ] ? [X]

Test substance: Citric Acid (77-92-9)

Reliability: Klimisch category 2

References: Al-Ani, F.Y. and Al-Lami, S.K. 1988. Absence of mutagenic activity of acidity regulators in the Ames *Salmonella*/microsome test. Mutat. Res. 206:467-470.

(i)

Type: Cytogenetic assay

System of testing: *S. cerevisiae* cells

Metabolic activation: With [ ]; Without [ ]; With and Without [X]; No Data [ ]

Results:

Genotoxic effects:

	+	?	-
With metabolic activation:	[ ]	[ ]	[X]
Without metabolic activation:	[ ]	[ ]	[X]

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
Ames test

GLP: Yes [ ] No [ ] ? [X]

Test substance: Citric Acid, Sodium Salt (994-36-5); Citric Acid, Tripotassium Salt (866-84-2)

Reliability: Klimisch category 2

References: Litton Bionetics Inc. 1975. Contract No. 223-74-2104 and FDA 71-268. In BIBRA. 1993. Toxicology Profile: Citric acid and its common salts. BIBRA International.

(j)

Type: Bacterial reverse mutation assay

System of testing: *Salmonella typhimurium* strains TA 92, TA 1535, TA 100, TA 1537, TA 94, and TA 98.

Concentration: maximum dose of 5.0 mg/plate

Metabolic activation: With [X]; Without [ ]; With and Without [ ]; No Data [ ]

Results:

Genotoxic effects:

	+	?	-
With metabolic activation:	[ ]	[ ]	[X]

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
An Ames test was conducted using monosodium citrate (18996-35-5) in a phosphate buffer. Six concentrations were tested. Two plates were used for each concentration.

GLP: Yes [ ] No [ ] ? [X]

Test substance: Monosodium citrate (18996-35-5), purity: 99.6%

Reliability: Klimisch category 2

References: Ishidate, M., Jr., Sofuni, T., Yoshikawa, K., Hayashi, M., Nohmi, T. Sawada, M., and Matsouka, A. 1984. Primary mutagenicity screening of food additives currently used in Japan. Fd. Chem. Toxic. 22(8):623-636.

(k)
Type: Bacterial gene mutation *(*Rec-assay)
System of testing: *Bacillus subtillus* strains H17 (Rec^+, arg^- ,and trp^-) and M45 (Rec^+, arg^-,and trp^-)
Concentration: 0.05 M
Results: < 5 mm distance (weakly positive)
Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
Each assay was repeated three times. An 0.05 aliquot of acetic acid, manganese salt (0.05 M) was dropped onto a 10 mm diameter filter paper disk. Plates were incubated at 37°C for 24 hours. The inhibition of growth is indicated by the distance (mm) between the edge of a paper disc and that of streaks. The difference between the inhibition zones for Rec^+ and Rec^- cells may be due to cellular repair. This is called "rec-effect".
GLP: Yes [ ] No [ ] ? [X]
Test substance: Acetic Acid, Manganese Salt (638-38-0),
Reliability: Klimisch category 2
References: Nishioka, H. 1975. Mutagenic activities of metal compounds in bacteria. Mutat. Res. 31:185-189.

B. Non-bacterial *in vitro* test

(a)
Type: Cytogenetic assay
Concentration: ≤16 mM
System of testing: Chinese hamster ovary K1 cells
Results: Acetic acid was not clastogenic at concentrations close to those showing cytotoxicity.
Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
CHO test guideline
GLP: Yes [ ] No [ ] ? [X]
Test substance: Acetic Acid (64-19-7)
Remarks: Low pH did induce some artificial chromosome aberrations, but these were eliminated by neutralization of the test medium.
Reliability: Klimisch category 2
References: Morita, T. Takeda, K., and Okumura, K. 1990. Mutat. Res. 240:195. In Clayton, G.D. and Clayton, F.E. (eds.). 1994. Patty's Industrial Hygiene and Toxicology. 4th Ed. Volume II, Part E: Toxicology. John Wiley & Sons, Inc.

(b)

Type:	Cytogenetic assay
System of testing:	Chinese hamster fibroblast cell line
Concentration:	maximum dose of 1 mg/ml
Metabolic activation:	With [ ]; Without [X]; With and Without [ ]; No Data [ ]
Results:	
Genotoxic effects:	+ ? -
	Without metabolic activation: [ ] [ ] [X]
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Substance was tested in a physiological saline solvent. Three different concentrations were tested and cells were exposed to each concentration for 48 hours.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Sodium Salt (127-09-3)
Reliability:	Klimisch category 2
References:	Ishidate, M., Jr., Sofuni, T., Yoshikawa, K., Hayashi, M., Nohmi, T. Sawada, M., and Matsouka, A. 1984. Primary mutagenicity screening of food additives currently used in Japan. Fd. Chem. Toxic. 22(8):623-636.

(c)

Type:	Cytogenetic assay
System of testing:	Chinese hamster fibroblast cell line
Concentration:	maximum dose of 0.5 mg/ml
Metabolic activation:	With [ ]; Without [X]; With and Without [ ]; No Data [ ]
Results:	
Genotoxic effects:	+ ? -
	Without metabolic activation: [ ] [ ] [X]
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Substance was tested in a physiological saline solvent. Three different concentrations were tested and cells were exposed to each concentration for 24 hours.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Fumaric Acid (110-17-8), purity: 99.7%
Reliability:	Klimisch category 2
References:	Ishidate, M., Jr., Sofuni, T., Yoshikawa, K., Hayashi, M., Nohmi, T. Sawada, M., and Matsouka, A. 1984. Primary mutagenicity screening of food additives currently used in Japan. Fd. Chem. Toxic. 22(8):623-636.

(d)

Type:	Cytogenetic assay
System of testing:	Chinese hamster fibroblast cell line
Concentration:	maximum dose of 1 mg/ml

Metabolic activation:	With [ ]; Without [X]; With and Without [ ]; No Data [ ]
Results:	
Genotoxic effects:	+ ? -
	Without metabolic activation: [ ] [ ] [X]
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Substance was tested in a physiological saline solvent. Three different concentrations were tested and cells were exposed to each concentration for 48 hours.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Malic Acid (6915-15-7)
Reliability:	Klimisch category 2
References:	Ishidate, M., Jr., Sofuni, T., Yoshikawa, K., Hayashi, M., Nohmi, T. Sawada, M., and Matsouka, A. 1984. Primary mutagenicity screening of food additives currently used in Japan. Fd. Chem. Toxic. 22(8):623-636.

5.6 GENETIC TOXICITY *IN VIVO*

(a)

Type:	Testicular DNA-synthesis inhibition test
Species/strain:	Mouse
Sex:	Female [ ]; Male [X]; Male/Female [ ]; No Data [ ]
Route of Administration:	gavage
Exposure period:	single application
Doses:	200, 500, and 1,000 mg/kg
Results:	No inhibitory effect on DNA-replication was detectable.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* 3H-thymidine incorporation was measured.
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Acetic Acid, Sodium Salt (127-09-3)
Remarks:	This is not a standard genotoxicity test system, but it provides evidence that acetic acid, sodium salt is not genotoxic in animals.
Reliability:	Klimisch category 2
References:	Seiler, J.P. 1981. The testicular DNA-synthesis inhibition test (DSI Test). In Short Tests Chem Carcinogen. In European Commission. 1996. Sodium acetate. International Uniform Chemical Information Database.

(b)

Type:	Dominant lethal assay
Species/strain:	Rat
Sex:	Female [ ]; Male [ ]; Male/Female [X]; No Data [ ]
Route of Administration:	Not stated
Exposure period:	5 days

Doses:	3 g/kg
Results:	No mutagenic potential was detected.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid (77-92-9)
Reliability:	Klimisch category 4
References:	Litton Bionetics, Inc. 1975. Contract No. FDA 71-268. In European Commission. 1996. Fumaric acid. International Uniform Chemical Information Database.

5.8 TOXICITY TO REPRODUCTION

(a)

Type:	Fertility [ ]; One-generation study [X]; Two-generation study [ ]; Other [ ]
Species/strain:	Guinea pig
Sex:	Female [ ]; Male [ ]; Male/Female [X]; No Data [ ]
Route of Administration:	oral in feed
Frequency of treatment:	daily
Doses:	1% (~ 400 mg/kg b.w./ day)
Control group:	Yes [ ]; No [X]; No Data [ ] Concurrent no treatment [ ]; Concurrent vehicle [ ]; Historical [ ]
NOEL Parental:	400 mg/kg bw/ day
NOEL F1 Offspring:	400 mg/kg bw/ day
Results:	There were no detectable toxic effects on growth, reproduction or lactation.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Two pregnant females received fumaric acid in their diet. Combined, they produced 12 offspring. The males were also fed fumaric acid in the diet.
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Fumaric Acid (110-17-8)
Reliability:	Klimisch category 4
References:	Levey, S. et al. 1946. J. Am. Pharm. Assoc. 35:298. In European Commission. 1996. Fumaric acid. International Uniform Chemical Information Database.

(b)

Type:	Fertility [X]; One-generation study [ ]; Two-generation study [ ]; Other [ ]
Species/strain:	Rat
Sex:	Female [X]; Male [ ]; Male/Female [ ]; No Data [ ]
Route of Administration:	oral in diet
Exposure period:	several months
Frequency of treatment:	daily
Doses:	600 mg/kg b.w

Control group:	Yes [ ]; No [ ]; No Data [X] Concurrent no treatment [ ]; Concurrent vehicle [ ]; Historical [ ]
NOAEL:	= 600 mg/kg bw
LOAEL:	>600 mg/kg bw
Results:	No reproductive effects detected.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Rats were fed diets containing 1.2% citric acid (about 600 mg/kg bw/ day). Exposure began 29 weeks prior to mating and continued for a few months after mating.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid (77-92-9)
Reliability:	Klimisch category 2
References:	Bonting and Jansen. 1956. Voeding 17:137. In European Commission. 1996. Citric acid. International Uniform Chemical Information Database. Also, In BIBRA. 1993. Toxicology profile: Citric acid and its common salts. BIBRA International.

(c)

Type:	Fertility [X]; One-generation study [X]; Two-generation study [ ]; Other [ ]
Species/strain:	Rat and mouse
Sex:	Female [X]; Male [ ]; Male/Female [ ]; No Data [ ]
Route of Administration:	oral in diet
Frequency of treatment:	daily
Doses:	5%
Control group:	Yes [ ]; No [ ]; No Data [X] Concurrent no treatment [ ]; Concurrent vehicle [ ]; Historical [ ]
Results:	No effects on reproduction, litter size or survival up to weaning were detected. A decrease in body weight gain and reduced survival time in mice were observed.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Female rats and mice were fed diets containing 5% citric acid (about 2.5 g/kg bw/day) before, during, and after mating.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid (77-92-9)
Remarks:	The effects on body weight gain and survival time may have resulted from the chelating ability of citric acid, which could impair absorption of calcium and iron.
Reliability:	Klimisch category 2
References:	Wright, E. and Hughes, R.E. 1976. Nutr. Rep. Int. 13:563. In Clayton, G.D. and Clayton, F.E. (eds.). 1994. Patty's Industrial Hygiene and Toxicology. 4th Ed. Volume II, Part E: Toxicology. John Wiley & Sons, Inc.

(d)

Type:	Fertility [X]; One-generation study [ ]; Two-generation study [ ]; Other [ ]
Species/strain:	Rat
Sex:	Female [X]; Male [ ]; Male/Female [ ]; No Data [ ]
Route of Administration:	oral in diet
Exposure period:	several months
Frequency of treatment:	daily
Doses:	0.1% citric acid, sodium salt
Control group:	Yes [ ]; No [ ]; No Data [X] Concurrent no treatment [ ]; Concurrent vehicle [ ]; Historical [ ]
NOAEL:	0.1% citric acid, sodium salt
LOAEL:	>0.1% citric acid, sodium salt
Results:	No reproductive effects detected at 0.1% citric acid, sodium salt.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Rats were fed diets containing 0.1% citric acid, sodium salt. Exposure began 29 weeks prior to mating and continued for a few months after mating.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid, Sodium Salt (994-36-5)
Reliability:	Klimisch category 2
References:	Bonting and Jansen. 1956. Voeding 17:137. In BIBRA. 1993. Toxicology profile: Citric acid and its common salts. BIBRA International.

5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

(a)

Species/strain:	Mouse
Sex:	Female [X]; Male [ ]; Male/Female [ ]; No Data [ ]
Route of Administration:	oral
Duration of the test:	17 days
Exposure period:	10 days
Frequency of treatment:	daily
Doses:	0, 16, 74, 345, and 1600 mg/kg bw/day
Control group:	Yes [X]; No [ ]; No Data [ ] Concurrent no treatment [X]; Concurrent vehicle [ ]; Historical [ ]
Results:	No effects on nidation or on maternal or fetal survival at doses up to 1600 mg/kg bw/day
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Following mating, adult female albino CD-1 mice were dosed daily by oral intubation beginning on day 6 of gestation. Animals were observed daily and body weights recorded for 10 days. On day 17, Caesarian sections were performed on all dams and the numbers of

	implantation sites, resorption sites, and live and dead fetuses was recorded. General external and internal examinations were also made of the dams.
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Acetic Acid (64-19-7)
Reliability:	Klimisch category 2
References:	Food and Drug Research Laboratories. 1974. Teratologic Evaluation of FDA 71-78 (Apple Cider Vinegar; Acetic Acid; Table Strength 5%) in Mice, Rats and Rabbits. NTIS PB234869.

(b)

Species/strain:	Rat
Sex:	Female [X]; Male [ ]; Male/Female [ ]; No Data [ ]
Route of Administration:	oral
Duration of the test:	14 days
Exposure period:	10 days
Frequency of treatment:	daily
Doses:	0, 16, 74, 345, and 1600 mg/kg bw/day
Control group:	Yes [X]; No [ ]; No Data [ ] Concurrent no treatment [X]; Concurrent vehicle [ ]; Historical [ ]
Results:	No effects on nidation or on maternal or fetal survival at doses up to 1600 mg/kg bw/day
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Following mating, adult female albino rats (Wistar) were dosed daily by oral intubation beginning on day 6 of gestation. Animals were observed daily and body weights recorded. On day 20, Caesarian sections were performed on all dams and the numbers of implantation sites, resorption sites, and live and dead fetuses was recorded. General external and internal examinations were also made of the dams.
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Acetic Acid (64-19-7)
Reliability:	Klimisch category 2
References:	Food and Drug Research Laboratories. 1974. Teratologic Evaluation of FDA 71-78 (Apple Cider Vinegar; Acetic Acid; Table Strength 5%) in Mice, Rats and Rabbits. NTIS PB234869.

(c)

Species/strain:	Rabbit
Sex:	Female [X]; Male [ ]; Male/Female [ ]; No Data [ ]
Route of Administration:	oral
Duration of the test:	23 days
Exposure period:	13 days
Frequency of treatment:	daily
Doses:	0, 16, 74, 345, and 1600 mg/kg bw/day

Control group:	Yes [X]; No [ ]; No Data [ ] Concurrent no treatment [X]; Concurrent vehicle [ ]; Historical [ ]
Results:	No effects on nidation or on maternal or fetal survival at doses up to 1600 mg/kg bw/day
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Following artificial insemination, adult Dutch-belted female rabbits were dosed daily by oral intubation beginning on day 6 of gestation. Animals were observed daily and body weights recorded. On day 29, Caesarian sections were performed on all does and the numbers of corpora lutea, implantation sites, resorption sites, and live and dead fetuses was recorded. General external and internal examinations were also made of the does.
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Acetic Acid (64-19-7)
Reliability:	Klimisch category 2
References:	Food and Drug Research Laboratories. 1974. Teratologic Evaluation of FDA 71-78 (Apple Cider Vinegar; Acetic Acid; Table Strength 5%) in Mice, Rats and Rabbits. NTIS PB234869.

(d)

Species/strain:	Mouse
Sex:	Female [X]; Male [ ]; Male/Female [ ]; No Data [ ]
Route of Administration:	oral
Exposure period:	5 days (days 8-12 of gestation)
Frequency of treatment:	daily
Post exposure observation period:	~ 2weeks
Duration of the test	~ 3 weeks
Doses:	1,000 mg/kg b.w.
Control group:	Yes [X]; No [ ]; No Data [ ] Concurrent no treatment [ ]; Concurrent vehicle [X]; Historical [ ]
NOEL Parental:	1,000 mg/ kg b.w.
NOEL F1 Offspring:	1,000 mg/kg b.w.
Results:	General parental toxicity: No effects Toxicity to offspring: No effects
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* 30 pregnant CD-1 mice, approximately 60 days old, were give a single oral dose by gavage on days 8-12 of gestation. Animal quarters were maintained at a temperature of 22 °C, a relative humidity of 40-60%, and a 7 am to 7 pm photoperiod.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Sodium Salt (127-09-3)
Reliability:	Klimisch category 2

References:	Kavlock, R.J., Short, R.D., Jr., and Chernoff, N. 1987. Further evaluation of an *in vivo* teratology screen. Teratog. Carcinog. Mutagen. 7:7-16.

(e)

Species/strain:	Fertile single-comb white leghorn chicken eggs
Route of Administration:	injection into egg
Frequency of treatment:	single injection
Doses:	maximum 10.0 mg/egg
Control group:	Yes [X]; No [ ]; No Data [ ] Concurrent no treatment [X]; Concurrent vehicle [X]; Historical [ ]
LD_{50}:	4.58 mg/egg
NOAEL teratogenicity:	10.0 mg/egg
Results:	No teratogenic response under any of the four test conditions was observed at the highest concentration injected.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Fertile eggs from single-comb white leghorn chickens were used. The test substance in water was administered by two routes, injection via the yolk and via the air cell. For each injection route, eggs were treated at two stages of incubation: preincubation (0 hrs) and on the fourth day (96 hrs). At least 100 embryos per each of four dose levels were treated. After treatment, all eggs were candled daily and nonviable embryos were removed. Surviving embryos were allowed to hatch.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Sodium Salt (127-09-3)
Remarks:	The LD_{50} is for the test condition in which the injection was made to the yolk sac at 0 hrs.
Reliability:	Klimisch category 3 (non-standard test organism)
References:	Verrett, M.J., Scott, W.F., Reynaldo, E.F., Alterman, E.K., and Thomas, C.A. 1980. Toxicity and teratogenicity of food additive chemicals in the developing chicken embryo. Toxicol Appl. Pharmacol. 56:265-273.

(f)

Type:	*Drosophila* embryonic cell culture test
Species/strain:	*Drosophila* (fruit fly)/Oregon R., Canton S_{109}, and Canton S
Doses:	10^{-3} M
Control group:	Yes [X]; No [ ]; No Data [ ] Concurrent no treatment [X]; Concurrent vehicle [ ]; Historical [ ]
Results:	The *in vitro* assay for fumaric acid was negative. There was no apparent teratogenic effect.

Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* *Drosophila* eggs were homogenized and the embryonic cells were plated out in cell culture dishes at 8 x 10^5 cells per ml of medium. After allowing time (15-20 min.) for cells to attach to the bottom of the dish, the medium covering the cells was replaced with medium in which the test substance had been dissolved. Embryonic cells were treated with an initial dose of 0.01 of the LD_{50} for adult female *Drosophila*. Cell and tissue differentiation was scored by counting the number of myotubes and neuron clusters (ganglia). An interference in normal cell differentiation (reduction in the number of myotubes and ganglia compared to the controls), was taken to be an indication of teratogenic response. A total of four dishes per trial were scored. The chemical was tested on three or more separate trials. A 50% reduction in the number of either myotubes and/or ganglia is taken as a teratogenic response.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Fumaric Acid (110-17-8)
Reliability:	Klimisch category 3 (non-standard study)
References:	Bournias-Vardiabasis, N. Teplitz, R.L., Chernoff, G.F., and Seecof, R., L. 1983. Detection of teratogens in the Drosophila embryonic culture test: Assay of 100 chemicals. Teratology 28:109-122.

(g)

Species/strain:	Fertile single-comb white leghorn chicken eggs
Route of Administration:	injection into egg
Frequency of treatment:	single injection
Doses:	maximum 10.0 mg/egg
Control group:	Yes [X]; No [ ]; No Data [ ] Concurrent no treatment [X]; Concurrent vehicle [X]; Historical [ ]
LD_{50}:	0.42 mg/egg
NOAEL teratogenicity:	10.0 mg/egg
Results:	No teratogenic response under any of the four test conditions was observed at the highest concentration injected.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Fertile eggs from single-comb white leghorn chickens were used. The test substance in water was administered by two routes, injection via the yolk and via the air cell. For each injection route, eggs were treated at two stages of incubation: preincubation (0 hrs) and on the fourth day (96 hrs). At least 100 embryos per each of four dose levels were treated. After treatment, all eggs were candled daily and nonviable

	embryos were removed. Surviving embryos were allowed to hatch.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Malic Acid (6915-15-7)
Remarks:	The LD_{50} for the test condition in which the injection was made to the air sac at 96 hrs.
Reliability:	Klimisch category 3 (non-standard study)
References:	Verrett, M.J., Scott, W.F., Reynaldo, E.F., Alterman, E.K., and Thomas, C.A. 1980. Toxicity and teratogenicity of food additive chemicals in the developing chicken embryo. Toxicol Appl. Pharmacol. 56:265-273.

(h)

Type:	Fertility [ ]; One-generation study [X]; Two-generation study [ ]; Other [ ]
Species/strain:	Rat and mouse
Sex:	Female [X]; Male [ ]; Male/Female [ ]; No Data [ ]
Route of Administration:	oral
Exposure period:	10 days (days 6-15 of pregnancy)
Frequency of treatment:	daily
Doses:	Rat: 350 mg/kg b.w. Mouse: 266 mg/kg b.w.
Control group:	Yes [X]; No [ ]; No Data [ ] Concurrent no treatment [X]; Concurrent vehicle [ ]; Historical [ ]
NOEL Parental:	Rat: 350 mg/kg b.w/day Mouse: 266 mg/kg b.w/day
Results:	No treatment-related fetal or maternal toxic effects or increases in fetal malformations were observed.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Pregnant rats and mice were given DL-malic acid by stomach tube at doses up to 350 and 266 mg/kg bw/ day, respectively, on days 6-15 of pregnancy.
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Malic Acid (6915-15-7)
Reliability:	Klimisch category 2
References:	Food and Drug Research Laboratories Inc. 1974. Teratologic evaluations of FDA 71-90 in mice and rats. Contract No. FDA 71-260. In BIBRA. 1992. Toxicology profile: Malic acid and its common salts. BIBRA International.

(i)

Species/strain:	Rat
Sex:	Female [X]; Male [ ]; Male/Female [ ]; No Data [ ]
Route of Administration:	oral
Duration of the test:	10 days
Exposure period:	days 6-15 of gestation
Frequency of treatment:	daily

Doses:	241 mg/kg b.w./day
Control group:	Yes [ ]; No [ ]; No Data [X] Concurrent no treatment [ ]; Concurrent vehicle [ ]; Historical [ ]
Results:	No indication of adverse effects on nidation (fertilization), maternal, or fetal survival.
NOAEL Maternal:	241 mg/kg b.w.
NOAEL Teratogenicity:	241 mg/kg b.w.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid (77-92-9)
Remarks:	No further data provided in reference.
Reliability:	Klimisch category 2
References:	Food & Drugs Research Laboratories, Inc. 1973. Teratologic evaluation of FDA 71-54. Contract No. 71-260. In European Commission. 1996. Citric acid. International Uniform Chemical Information Database.

(j)

Species/strain:	Fertile single-comb white leghorn chicken eggs
Route of Administration:	injection into egg
Frequency of treatment:	single injection
Doses:	maximum 10.0 mg/egg
Control group:	Yes [X]; No [ ]; No Data [ ] Concurrent no treatment [X]; Concurrent vehicle [X]; Historical [ ]
LD_{50}:	2.06 mg/egg
NOAEL teratogenicity:	10.0 mg/egg
Results:	No teratogenic response under any of the four test conditions was observed at the highest concentration injected.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Fertile eggs from single-comb white leghorn chickens were used. The test substance in water was administered by two routes, injection via the yolk and via the air cell. For each injection route, eggs were treated at two stages of incubation: preincubation (0 hrs) and on the fourth day (96 hrs). At least 100 embryos per each of four dose levels were treated. After treatment, all eggs were candled daily and nonviable embryos were removed. Surviving embryos were allowed to hatch.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid, Sodium Salt (994-36-5)
Remarks:	The LD_{50} is for the test condition in which the injection was made into the air sac at 96 hrs.
Reliability:	Klimisch category 3 (non-standard study)

References:	Verrett, M.J., Scott, W.F., Reynaldo, E.F., Alterman, E.K., and Thomas, C.A. 1980. Toxicity and teratogenicity of food additive chemicals in the developing chicken embryo. Toxicol Appl. Pharmacol. 56:265-273.

(k)

Species/strain:	Fertile single-comb white leghorn chicken eggs
Route of Administration:	injection into egg
Frequency of treatment:	single injection
Doses:	maximum 10.0 mg/egg
Control group:	Yes [X]; No [ ]; No Data [ ] Concurrent no treatment [X]; Concurrent vehicle [X]; Historical [ ]
LD_{50} (Air cell; 0 hrs):	>10.0 mg/egg
LD_{50}(Air cell, 96 hrs):	1.47 mg/egg
LD_{50}(Yolk sac, 0 hrs):	>10.0 mg/egg
LD_{50}(Yolk sac, 96 hrs):	Estimated to be 12.09 mg/egg by extrapolation on the regression line.
Results:	Air cell treatment at preincubation resulted in a high incidence of birds with hypopigmentation of the down. Air cell treatment on the fourth day resulted in a high incidence of birds with severe abnormalities at all 3 test levels that allowed some to hatch. The defects involved primarily the beak, eyes, and eyelids.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Fertile eggs from single-comb white leghorn chickens were used. The test substance in water was administered by two routes, injection via the yolk and via the air cell. For each injection route, eggs were treated at two stages of incubation: preincubation (0 hrs) and on the fourth day (96 hrs). At least 100 embryos per each of four dose levels were treated. After treatment, all eggs were candled daily and nonviable embryos were removed. Surviving embryos were allowed to hatch.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Manganese Salt (638-38-0)
Remarks:	The author considers the hypopigmentation of down to be a toxic effect rather than a teratogenic one.
Reliability:	Klimisch category 3 (non-standard study)
References:	Verrett, M.J., Scott, W.F., Reynaldo, E.F., Alterman, E.K., and Thomas, C.A. 1980. Toxicity and teratogenicity of food additive chemicals in the developing chicken embryo. Toxicol Appl. Pharmacol. 56:265-273.

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